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Dose-related Effects of Salvinorin A in Humans: Dissociative, Hallucinogenic, and Memory Effects

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Abstract

Rationale—Salvinorin A is a kappa opioid agonist and the principal psychoactive constituent of the plant *Salvia divinorum,* which has increased in popularity as a recreational drug over the past decade. Few human studies have examined salvinorin A.

Objective—This double-blind, placebo-controlled study evaluated the dose-related effects of inhaled salvinorin A in individuals with histories of hallucinogen use.

Methods—Eight healthy hallucinogen-using adults inhaled up to 16 doses of salvinorin A (0.375 - 21 μg/kg) in ascending order. Physiological, behavioral, and subjective effects were assessed every 2 min for 60 min after administration. Qualitative subjective effects were assessed retrospectively via questionnaires at the end of sessions. Persisting effects were assessed 1 month later.

Results—Orderly dose-related effects peaked at 2 min and then rapidly dissipated, replicating previous findings. Subjective effects were intense, with maximal drug strength ratings or unresponsiveness frequently observed at high doses. Questionnaires assessing qualitative effects (Hallucinogen Rating Scale, Pharmacological Class Questionnaire) suggested some overlap with serotonergically mediated classic hallucinogens. Salvinorin A also produced dose-related dissociative effects and impairments in recall/recognition memory. At 1-month follow-up, there was no evidence of persisting adverse effects. Participants reported salvinorin A effects were qualitatively different from other drugs.

Conclusions—Salvinorin A produces a unique profile of subjective and cognitive effects, including strong dissociative effects and memory impairment, which only partially overlap with classic hallucinogen effects. Along with nonhuman studies of salvinorin A, these results are important for understanding the neurobiology of the kappa opioid system and may ultimately have important therapeutic applications.

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Keywords

salvinorin A; *Salvia divinorum*; kappa opioid agonist; hallucinogen; psychedelic; dissociative; human

INTRODUCTION

Salvinorin A is the principal psychoactive constituent of *Salvia divinorum,* a member of the mint family that has been used historically in ethnomedical practices in Mexico (Siebert 1994; Ott 1995; Ott 1996; Valdes et al. 2001) and has gained increased popularity as a recreational drug (Wu et al., 2011; Perron et al., 2012). Salvinorin A is a unique hallucinogenic compound: It is a nonnitrogenous selective kappa opioid agonist with no activity at the 5-HT_{2A} serotonin receptor, the principal site of activity of classic hallucinogens (Roth et al. 2002; Prisinzano 2005; Cunningham et al. 2011). Nonhuman research studies have characterized the pharmacological, behavioral, and discriminative effects of *S. divinorum* and salvinorin A (Vortherms and Roth 2006; Cunningham et al. 2011), and there is interest in using salvinorin A and related compounds to study kappa-opioid mechanisms in neurological disorders (e.g., Alzheimer's disease), psychiatric disorders, pain, and drug dependence (Mello and Negus 2000; Sheffler and Roth 2003; Morani et al. 2009; Kivell and Prisinzano 2010; Cunningham et al. 2011; Tejeda et al. 2012). However, few human laboratory studies have demonstrated reliable effects (Johnson et al. 2011; Addy 2012; Ranganathan et al., 2012; *cf*, no effects of sublingual salvinorin A in Mendelson et al. 2011). In the present double-blind, placebo-controlled study ($N = 8$), we extend some preliminary observations in four volunteers (Johnson et al., 2011) and characterize the effects of salvinorin A on new outcome measures, including a 1-month follow-up assessment, with a focus on identifying the unique and overlapping effects of salvinorin A compared to classic hallucinogens and other pharmacological drug classes.

Most information about the effects of *S. divinorum* in humans has come from survey studies and qualitative interviews of *S. divinorum* users. Survey respondents are in general agreement that the effects of *S. divinorum* are "intense" and "unique" compared to other drugs or methods for inducing alterations in consciousness (Albertson and Grubbs 2009; Baggott et al. 2010; Kelly 2011; Sumnall et al. 2011). Elevations in scores on the Hallucinogen Rating Scale (HRS) (Gonzalez et al., 2006; Albertson and Grubbs 2009) suggest some overlap with the subjective effects of classic serotonergic hallucinogens (Strassman et al. 1994; Griffiths et al. 2006; Griffiths et al. 2011), However, less than a quarter of respondents across studies report that *S. divinorum* is similar to classic hallucinogens (Albertson and Grubbs 2009; Baggott et al. 2010). Results are mixed regarding the similarity of *S. divinorum* to cannabis (6.5%, Baggott et al. 2010; 44%, Albertson and Grubbs 2009). There is little evidence of *S. divinorum* causing psychological dependence or psychiatric dysfunction beyond acute effects (Sumnall et al. 2011), with mixed reports of positive antidepressant-like effects (Hanes 2001; Baggott et al. 2010) and negative effects such as "mental cloudiness" lasting 24 hours or more after use (Kelly 2011). Most respondents indicate that they use *S. divinorum* for recreation or entertainment (Albertson and Grubbs 2009; Kelly 2011), while some individuals indicate spiritual reasons for use (Baggott et al. 2010).

Results from a double-blind, placebo-controlled study of salvinorin A in hallucinogen-experienced adults (Addy 2012) are consistent with these survey findings. The active condition (1017 μg salvinorin A) vs. the placebo condition (100 μg salvinorin A) increased HRS ratings, including somatosensory, perceptual, affective and cognitive effects, indicating overlap with the subjective effects of serotonergic hallucinogens. However, participants

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were more likely to compare salvinorin A effects to dreaming (43%) than to classic hallucinogens (e.g., 13% LSD, 10% psilocybin), dissociative hallucinogens (7%) or marijuana (10%). Eight-week follow-up data indicated a mix of positive and negative effects lasting more than 24 hours after inhalation, including increases in positive mood, empathy, and aesthetic sensitivity as well as headache, fatigue, and difficulty concentrating.

A previous report from our laboratory (Johnson et al. 2011) provided an initial demonstration in 4 participants of the safety, tolerability, and time course of vaporized/inhaled salvinorin A across multiple doses, from sub-threshold (0.375 μg/kg) to high (21 μg/kg). These preliminary results showed consistent time- and dose-related effects on participant ratings of overall drug strength, indicating the reliability of the vaporization/inhalation procedure. Dose-related increases on the HRS and the Mysticism Scale (a measure of mystical-type subjective effects that has been shown sensitive to psilocybin; Griffiths et al. 2006; Griffiths et al. 2011) suggested phenomenological overlap with classic hallucinogens. However, participants uniformly reported that salvinorin A produced unique effects that were not typical of other hallucinogens they had used. The aim of the present report was twofold: 1) to extend our preliminary findings to the full study sample ($N = 8$) and, 2) to characterize the effects of salvinorin A on a range of outcome measures not previously reported, including monitor ratings of drug effects (e.g., dissociation), participant ratings of qualitative subjective effects, a test of recall and recognition memory, and a 1-month follow-up assessment of psychological function.

METHODS

Participants

Preliminary data on a sub-set of outcome measures were reported previously for the first 4 participants who completed the study (Johnson et al., 2011) (see Online Resources 1 and 2 for measures). The present study includes the full study sample of 8 participants ($M = 26.8$ years old, range = 21 – 35 years old; 3 female) who passed the in-person medical and psychiatric screening (details in Johnson et al. 2011) and subsequently completed the drug sessions and data collection; an additional 4 individuals did not pass the in-person screening. Participants reported previous lifetime use of classic hallucinogens ($M = 78$ occasions, range = 5 - 412) and use of *S. divinorum* at least once in the past five years ($M = 10$ occasions, range = 1 - 40). Participants agreed to refrain from using *S. divinorum* or illicit drugs during the course of the study. Participants were compensated approximately $2000 for completing all sessions and laboratory assessments. The Institutional Review Board of the Johns Hopkins University School of Medicine approved the study, and all participants gave their informed consent before participation.

Salvinorin A Sessions

Doses of salvinorin A (0.375 - 21 μg/kg, adjusted for bodyweight) were administered in an ascending order, with a single placebo session inserted in a random position among each consecutive block of 5 sessions. Each participant completed up to 20 sessions (16 salvinorin A doses and 4 placebo doses) across several weeks, with consecutive sessions separated by at least 1 day. Participants were told that on any session they would receive either a dose of salvinorin A or placebo but were not told about the ascending design or frequency of placebo administration. On each session, the participant inhaled slowly for 40 s while a flask containing salvinorin A was heated, followed by a verbally cued exhale. Participants were seated in a comfortable, semi-upright posture, wore eyeshades, and listened to a relaxing instrumental music track throughout the session. Details of the vaporization/inhalation procedure and session protocol can be found in Johnson et al., 2011.

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Session-day Measures

Measures Collected Throughout each Session—The following measures were collected at baseline and every 2 minutes for 60 minutes after drug administration: blood pressure and heart rate (Non-Invasive Patient Monitor Model 507E, Criticare Systems, Waukesha, WI), verbally-cued participant ratings of drug strength (0 = definitely no effect; 1 or 2 = possible salvinorin A effects; 3 - 10 = definite salvinorin A effects with 10 representing “the strongest effect imaginable for salvinorin A”), and blinded monitor ratings of drug effects (0 = no effect, 4 = strong effect; Overall Drug Effect, Unresponsiveness, Anxiety/fear, Distance from Usual Daily Reality, Paranoia, Motor activity, Visual effects, Joy/peace, Psychological distress, and Physical distress). Resting and kinetic tremor were rated on a 5-point scale (Fahn-Tolosa-Marin Tremor Rating Scale, Fahn et al. 1993) approximately 5 minutes before and at 15 and 30 minutes after drug administration.

Word Recall and Recognition—The effect of salvinorin A on recall and recognition was assessed by an auditory memory task. For each session, 12 one-syllable words were selected at random (without replacement) from a set of 252 words, which were matched for Thorndike-Lorge written frequency and concreteness (MRC Psycholinguistic Database 2.0: http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm). Three of the 12 words were presented during the session and the remaining 9 words served as distracters during the subsequent assessment of recognition. All participants were presented the same set of words for each session (e.g., “judge”, “hill”, “dance” as target words on Session 7). At each of three time points following drug administration (at 2, 4, and 6 minutes), the blinded session monitor verbally announced one of the three words (e.g., “The word is hill.” [~1 s pause] “Hill.”). At 15 minutes after drug administration, recall was assessed by asking the participant to list the 3 words that he/she remembered hearing at the previous time points. To assess recognition, the session monitor then read aloud the list of 12 one-syllable words, and the participant indicated whether he/she remembered hearing each word by saying “yes” or “no” following each word. Outcome measures for each session were number of words correctly recalled (range = 0 - 3), recognition accuracy (d’) and recognition response bias (C) (Snodgrass and Corwin 1988).

End-of-Session Measures—At the end of each session, participants completed retrospective ratings of overall drug strength (0 = definitely no effect; 10 = “the strongest effect imaginable for salvinorin A”), Liking and Disliking of the drug effect (2 questions; 0= neutral or no effect, 4=like (or dislike) very much), and overall Good Effects and Bad Effects (2 questions; 0= no good (or bad) effects at all, 4=very much). Participants also completed several questionnaires of qualitative subjective effects. The short form of the Addiction Center Research Inventory (ARCI, 5 subscales; Martin et al. 1971; Jasinski 1977) has been used in previous studies to assess a range of subjective effects associated with various classes of drug. The Hallucinogen Rating Scale (HRS, 6 subscales; Strassman et al. 1994) and the APZ (3 subscales; Dittrich 1998) have been used in previous studies to assess the effects of classic hallucinogens (Griffiths et al. 2006; Griffiths et al. 2011; Studerus et al. 2011). The Mysticism Scale (Hood et al. 2001) and the States of Consciousness Questionnaire (SOCQ, 6 subscales; Pahnke 1969) have been used in previous studies to assess the mystical-type effects of hallucinogens (Turek et al. 1974; Richards et al. 1977; Griffiths et al. 2006; Griffiths et al. 2011; Reissig et al. 2012). The Perception Scale (10 subscales; Isbell et al. 1956) has been used to assess the effects of kappa opioid agonists (Kumor et al. 1986; Walsh et al. 2008). The State subscale of the State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1983) was used as a measure of transient anxiety.

The similarity of salvinorin A to other drug classes was assessed by the Quantitative Pharmacological Class Questionnaire (QPCQ; Reissig et al. 2012). Participants completed a

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series of visual-analogue scale ratings (0 = “no, not at all”, 100 = “yes, very much”) indicating how similar the session-day effects were to each of 15 classes of drugs (e.g., “How much did today’s drug effect feel like CANNABIS?”). The 15 drug classes were Classic Hallucinogen, Dissociative anesthetic Hallucinogen, Cannabis, Nitrous oxide, Alcohol, Sedative Hypnotic, Opioid, Caffeine, Stimulant, Nicotine, MDMA, Inhalant, Ephedrine, Muscle Relaxant, and GHB. Fewer than 3 participants reported lifetime use of inhalants, muscle relaxants, ephedrine, or GHB at screening; thus, these drug classes were not analyzed.

Participants wrote an open-ended narrative of subjective effects after each session; most reports were submitted to the study staff within 1-2 days after the session. Reports were reviewed in order to identify consistent themes that were not well represented by the quantitative measures.

Follow-up Assessment

About 1 month after completing the final salvinorin A session, participants returned to the laboratory to complete a follow-up assessment that included questionnaires, an open-ended narrative on study experiences, and clinical interviews with at least two study staff. Standardized measures were used to assess changes from baseline to follow-up on various dimensions of psychological function, including depressive symptoms (Beck Depression Inventory, BDI; Beck et al. 1996), trait anxiety (STAI; Spielberger et al. 1983), affective mood state (Profile of Mood States, POMS; McNair et al. 1971), and psychiatric symptoms (Brief Symptom Inventory, BSI; Derogatis and Melisaratos 1983; Derogatis 1993). In addition, because there have been reports of prolonged or recurring perceptual changes in some hallucinogen users (Baggott et al. 2011), we assessed the frequency of 12 types of visual perceptual events (e.g., afterimages, apparent movement in stationary objects).

Changes in attitudes, moods and behaviors were assessed via the Persisting Effects Questionnaire (143 items), which includes questions about overall personal meaning and spiritual significance. Consistent with previous studies (Griffiths et al. 2006; Griffiths et al. 2011; Reissig et al. 2012), participants were instructed to complete the questionnaire in reference to any changes they attributed to study participation. We also obtained baseline and follow-up ratings of behaviors, moods, and attitudes (e.g., patience, optimism, anxiety, negative expressions of anger) from community observers (i.e., friends and family members) during a structure telephone interview (see Griffiths et al. 2006 for scoring). For one participant we obtained complete data from only 1 rater. For the remaining participants, data from 2 raters were averaged at each assessment.

Analysis

Two male participants answered “yes” to the tolerability question at the end of their 19.5 μg/kg session (“Would you absolutely refuse to receive the same or higher dose of today’s drug in future sessions?”) and were not administered the 21 μg/kg dose. Thus, complete data were available for 15 dose levels of salvinorin A (maximum dose = 19.5 μg/kg). For each participant, ratings across the placebo sessions were averaged to create a single placebo data point. In cases in which the participant was unresponsive during the first few minutes of drug effects, the value of ‘10’ was imputed for participant-rated drug strength.

Data on the ARCI and word recall task were missing for 1 male participant, leaving $N = 7$ available for analysis. On the word recall task, single-session data were missing for 1 female participant for 2 sessions (0.375 and .75 μg/kg) and 1 male participant for 1 session (0.375 μg/kg).

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The majority of the session-day outcomes were analyzed using repeated measures regression (PROC MIXED, AR(1) covariance structure; SAS 9.2) with within-subjects factor of Dose (16 dose levels including placebo). Dunnett's pairwise comparisons were conducted to compare each dose to placebo ($p < .05$). For each questionnaire with multiple subscales, total and subscale scores were analyzed independently. For measures collected at multiple time points during the drug sessions (physiology measures, participant and monitor ratings of drug effects), analyses were conducted on peak ratings (i.e., the maximum rating across all time points within a session). Linear regression (IBM SPSS Statistics Version 19.0) was used to model dose-related effects in the word recall task and the QPCQ. Changes from baseline to follow-up (e.g., in psychiatric symptoms) were assessed by paired *t* tests. Descriptive results are reported for the Persisting Effects Questionnaire and the community observer ratings.

RESULTS

Session-day Measures

Drug Strength—Consistent with our previous findings (Johnson et al., 2011), orderly time- and dose-related effects were observed, with participant-rated drug strength peaking at 2 minutes (first time point) and then rapidly and progressively decreasing toward pre-inhalation levels (**Online Resource 1**). Peak drug strength (i.e., maximum rating across all time points in each session) showed orderly dose-related increases for participant ($F(15, 105) = 7.92$, $p < .001$) and monitor ($F(15, 105) = 3.38$, $p < .001$) ratings that appeared quite linear from 0.375-19.5 μg/kg (Figure 1a). Participant end-of-session ratings showed similar dose-related increases ($F(15, 105) = 10.8$, $p < .001$; Table 1).

Four participants (2 male) provided the maximal rating of 10 and five participants (4 male) were unresponsive (scores imputed as 10) on at least one time point for at least one dose. Two participants (1 female) showed apparent dissociation for brief periods (e.g., more frequent movement and unusual movement compared to other sessions, and unintelligible verbalizations, with little memory for effects during that period) at doses greater than 15.0 μg/kg.

Physiological Effects—The effects of Dose on blood pressure and heart rate were not significant (*p*s > .10; Online Resource 2). No resting or kinetic tremors were observed at baseline or at the 30-min time point during any session. At the 15-min time point, 1 male participant had slightly elevated observer ratings (1 = possibly slight, intermittent) for resting tremor (at 2 doses: 6.0 μg/kg and 10.5 μg/kg) and kinetic tremor (at 10.5 μg/kg).

Monitor Ratings of Drug Effects—Monitor ratings (peak rating for each dimension) showed robust dose-related increases in Distance from Usual Daily Reality ($F(15, 105) = 2.92$, $p = .001$) and Unresponsiveness ($F(15, 105) = 1.81$, $p = .043$) (see Figure 1b). The effect of Dose was also significant for ratings of Motor Activity ($F(15, 105) = 1.81$, $p = .043$) and Psychological Distress ($F(15, 105) = 2.44$, $p = .004$). The effect of Dose was not significant (*p*s > .10) for the remaining dimensions (Joy/peace, Anxiety/fear, Paranoia, Visual Effects, and Physical Distress), which showed generally low ratings across all sessions.

End-of-Session Measures

Liking/good effects: Ratings of drug liking and good effects increased steadily across dose, similar to the pattern observed for ratings of peak drug strength (Table 1). The effect of Dose was significant for liking ($F(15, 105) = 3.65$, $p < .001$) and a trend for good effects ($F(15, 105) = 1.74$, $p = .054$). Mean ratings of drug disliking ($M = 0.20$, range = 0 - 2) and

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bad effects (M = 0.16, range = 0 - 2) were low across all sessions, and there was no significant effect of Dose for either measure (ps > .50).

Questionnaires of classic hallucinogen effects: There were significant effects of Dose on measures of classic hallucinogen effects (HRS, APZ) and mystical-type effects (Mysticism Scale, SOCQ). Posthoc comparisons indicated that total scores and the majority of the subscale scores were significantly greater than placebo at moderate and high dose levels (Table 1).

Perception Scale: Results for the Perception Scale, a presumed measure of kappa-opioid effects, indicated significant dose-effects for total score and some of the subscales (General, Detachment, Cognitive, Paranoia). Among the subscales, Detachment showed significant elevations above placebo for all doses 4.5 μg/kg and higher (Table 1).

ARCI: Results for the ARCI indicated significant dose-related increases only for Benzedrine Group (BG), a measure of intellectual efficiency. However, scores did not show an orderly pattern across doses, and posthoc comparisons with placebo were not significant. Scores on the remaining scales were not significant (Dose ps > .20; Table 1).

STAI: Ratings of state anxiety (possible range = 20 - 80) were low (placebo, M = 30.4; 10.5 μg/kg, M = 30.1; 19.5 μg/kg , M = 29.8) and were not significant (Dose p = .15).

Quantitative Pharmacological Class Questionnaire (QPCQ): Independent regression analyses were conducted to test the effect of Dose on session-day ratings of similarity (visual analogue = 0 - 100 mm) for each drug class. The only drug class that showed significant increases in similarity ratings across dose was Classic Hallucinogen (ß = .34, R^2 = .11, p < .001). However, ratings for Classic Hallucinogen were low on average (< 30 out of 100) and highly variable across participants (range = 0 - 100), even at moderate and high doses. At each of the two highest doses (18.0 and 19.5 μg/kg), only 2 participants provided similarity ratings greater than 75 out of 100 while 5 participants provided similarity ratings less than 25 out of 100. Two drug classes showed significant dose-related decreases: Caffeine (ß = −.23, R^2 = .05, p = .009), and Stimulant (ß = −.21, R^2 = .04, p = .021). However, overall ratings for Caffeine and Stimulant were extremely low across all doses of salvinorin A (maximum rating = 8 out of 100).

Word Recall and Recognition—Dose was strongly negatively correlated with number of words recalled (r(110) = −.49, p < .001) and recognition accuracy (d') (r(109) = −.42, p < .001), and weakly positively correlated with recognition response bias (C) (r(109) = .24, p = .012) (i.e., a conservative bias: increased likelihood of answering "no" as dose increased). These group-level correlations were individually confirmed in 6 of the 7 participants for word recall (rs = −.33 to −.81) and d' (rs = −.47 to −.78); 1 participant showed no dose effects on either measure ($r \approx 0$).

Step-wise linear regression was used to model the effect of Dose on word recall and d' at the group level (up to 16 dose levels for each of 7 participants). In each regression model, performance (word recall or d', respectively) at baseline (i.e. mean placebo data) was included in the first step to control for baseline memory ability, and Dose was tested as a predictor in the second step. Dose explained significant variance in session-day word recall (ß = −.50, ΔR^2 = .25, p < .001) and d' (ß = −.43, ΔR^2 = .18, p < .001) over and above memory performance at baseline, indicating dose-related impairments in recall and recognition memory.

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Open-ended Narratives of Session-day Experiences—Within about 1-3 days after each salvinorin A session, participants wrote an open-ended narrative about subjective effects and reflections on the session experience. Five themes, which we noted in our previous report (Johnson et al. 2011), were consistently represented in the full sample: disruptions in vestibular and interoceptive signals, contact with entities, revisiting childhood memories, cartoon-like imagery, and recurring content across sessions (see Table 2 for representative descriptions). All participants described specific alterations of their body in space, such as being dragged, pulled, or pushed in a particular direction ($n = 7$) and spinning/flipping, twisting or stretching ($n = 5$). All participants reported encounters with entities or beings, which often included communication and interaction. The somewhat overlapping themes of "cartoon-like imagery" and "childhood memories" were each evident in six participants. Five participants reported specific visual or auditory phenomena that they associated with childhood, such as cartoon-like images and/or auditory content (e.g., verbal cues from the monitor were heard as sing-along songs from children's animations). Three participants reported re-experiencing specific, autobiographical events from childhood and five participants reported vividly experiencing a scene (e.g., being at a carnival or fair, $n = 2$; being in a classroom, $n = 3$) that they associated with childhood but could not identify as a specific episodic memory. Finally, 6 participants reported strikingly similar content and subjective effects across multiple sessions.

Follow-up Assessment

There were no significant changes (ps > .20) between screening and follow-up in depressive symptoms (BDI: $M = +2.0$), anxiety (STAI: $M = +1.8$), affective mood state (POMS: Vigor, $M = -2.0$; Fatigue, $M = +1.0$; Confusion, $M = +2.25$), psychiatric symptoms (BSI: $M = +9.9$), or visual disturbances ($M = +0.75$). One male participant was greater than 2 SD from the group mean change on the BSI (+71). Study staff confirmed through clinical interviews that the participant was not at risk either medically or psychologically, and the participant did not attribute the symptoms to study participation.

Participants rated the salvinorin A sessions as personally meaningful ($M = 4.9$, range = 4 - 6, where 5 = "similar to meaningful experiences that occur on average once every 5 years") and spiritually significant ($M = 3.6$, range = 1 – 5, where 4 = "very much"). Modest changes were observed in overall well-being ($M = 1.5$, where 1 = slight and 2 = moderate) and ratings of change on 12 dimensions of positive (Ms = 27 to 40% of maximum possible score) and negative (Ms = 0 to 7% of maximum possible score) attitudes, mood and behaviors. Nearly all of the hallucinogen-experienced participants found salvinorin A to be "somewhat" ($n = 2$) or "completely" ($n = 5$) unique compared to other meaningful life experiences.

In open-ended reports, no participant indicated lasting negative effects from the sessions. Four participants reported specific positive changes that they attributed to the session-day experiences, including increased self-confidence, a sense of enhanced physical comfort and calm, less emotional reactivity, improvements in interpersonal relationships, and renewed interest in daily responsibilities (career pursuits).

Community observer ratings indicated similar slight increases in overall well-being ($M = +1.1$, range = 0 to +2.5) and positive behaviors, moods, and attitudes (mean across 13 dimensions was +4.54, range = −3.0 to +15.5). Ratings of overall behavior change (separate question) indicated either no change (1 participant) or positive change (7 participants).

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DISCUSSION

This double-blind, placebo-controlled study of vaporized/inhaled salvinorin A in 8 hallucinogen-experienced adults demonstrated reliable time- and dose-related effects on subjective measures, observer ratings, and an objective measure of recall/recognition memory. Blood pressure, heart rate, and tremor were unaffected across doses. Notably, 50% of participants provided the maximal rating of 10 (strongest effect imaginable for this drug) at one or more time points during at least one session and two participants reached a voluntary stopping point at the second-highest dose (19.5 μg/kg). We recommend that human research with high doses of salvinorin A include psychiatric screening, support and monitoring during acute drug effects, and follow-up to assure safety (Johnson et al. 2008).

Ratings on end-of-day subjective effects measures indicated a moderate degree of overlap with classic serotonergic hallucinogens at high doses, including somatosensory, perceptual, cognitive, and mystical-type effects (Table 1). In contrast to a previous survey of *S. divinorum* users (Gonzalez et al., 2006), the ARCI scales did not show dose-related sensitivity to salvinorin A. Ratings of overall similarity to classic hallucinogens (on the Quantitative Pharmacological Class Questionnaire) increased linearly as a function dose. However, average ratings of similarity were relatively low (< 30 out of 100), indicating that participants judged salvinorin A to be only somewhat similar to classic hallucinogens. As in previous survey studies (Albertson and Grubbs 2009; Baggott et al. 2010; Kelly 2011), participants reported that the effects of salvinorin A were unique and particularly intense compared to other hallucinogens they had used.

Dissociative effects were pronounced at moderate and high doses, including dose-related increases in monitor ratings of Distance from Usual Daily Reality and Unresponsiveness, and in participant ratings of Detachment (Perception Scale) and lack of awareness of normal time and space (SOCQ) (Table 1). In addition, dose-related impairments in word recall and recognition were observed for an auditory memory task in all except 1 participant. In support of these quantitative results, 5 participants were completely unresponsive to the session monitor's verbal cues (e.g., for drug strength) during peak drug effects on one or more sessions. Particularly strong dissociative effects were observed in two participants (at doses higher than 15.0 μg/kg), who exhibited erratic motor movements, appeared to have no awareness of the surrounding environment during peak effects, and reported no memory of their behavioral responses once drug effects subsided. These reactions are consistent with some of the more chaotic effects observed in online videos of *S. divinorum* users (Lange et al. 2010) and highlight the potential for erratic behavior or accidents when *S. divinorum* is administered in uncontrolled conditions.

In addition to hallucinogenic and dissociative effects, salvinorin A produced a pattern of subjective effects suggestive of possible abuse liability. Ratings of "liking" and "good" effects increased across doses while ratings of "disliking", "bad effects" and anxiety (STAI) were low and not significantly affected by dose. About half of the participants exhibited positive affect (audible laughter) during peak drug effects. These data are some of the first human laboratory findings indicating that salvinorin A has some abuse liability. Although the positive mood effects may be specific to the present sample of experienced hallucinogen users, the results are consistent with results from surveys of *S. divinorum* users (Baggott et al. 2010; Sumnall et al. 2011), and some data in nonhumans (conditioned place preference in Braida et al., 2007; Braida et al., 2008; *cf.* Conditioned place avoidance in Zhang et al., 2005). It may be valuable for future studies to measure dose-related changes in positive and negative affect and emotions, as well as to directly assess self-administration or preference to characterize the reinforcing effects of salvinorin A in participants with varying degrees of lifetime drug use.

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In spite of intense acute effects of salvinorin A across numerous sessions, follow-up assessments showed no evidence of lasting negative effects such as depression, anxiety, psychiatric symptoms, or visual disturbances. While no prior study has systematically investigated adverse reactions in persons with documented, repeated exposures, our findings are consistent with survey studies that have found little evidence of persisting psychiatric symptoms (Sumnall et al. 2011; Baggott et al. 2011). Participants generally viewed the session experiences as personally meaningful and reported modest increases in positive attitudes, moods and behaviors, although not to the same degree as participants in studies of psilocybin (Griffiths et al. 2006; Griffiths et al. 2011) and dextromethorphan (Reissig et al., 2012). The interpretation of these results is necessarily limited as the participant sample was small and homogeneous, and there was no control group. However, the findings suggest that exposure to salvinorin A in a supportive, medical research context does not have lingering negative health consequences.

The most consistent finding across human studies of salvinorin A and *S. divinorum* is that the majority of participants find the subjective effects of the drug to be unique compared to other pharmacological classes of drugs, including classic hallucinogens (Albertson and Grubbs 2009; Baggott et al. 2010; Kelly 2011; Addy 2012). Thus, existing measures of subjective effects (HRS, APZ, Mysticism Scale, ARCI) may have limited utility in quantifying kappa-opioid effects. In addition to using standard outcome measures in the present study, we attempted to identify unique subjective effects by conducting an informal review of participants' open-ended narratives. This approach revealed five consistent themes across sessions: disruptions in vestibular and interoceptive processing (e.g., feeling of movement in a particular direction, spinning, stretching), communication and interaction with entities or beings, revisiting childhood memories, cartoon-like visual imagery and auditory experiences (often associated with childhood), and recurring content across sessions. The themes are consistent with *S. divinorum* users' open-ended reports in previous studies (Kelly 2011; Addy 2012). Kappa opioid receptors have widespread distribution in brain regions involved in interoception, reward, pain, emotion, and memory (Mansour et al. 1988; Merrer et al. 2009; Tijeda et al. 2012), and future neuroimaging studies should be able to elucidate the underlying neural representations of specific subjective effects. It should also be possible to compare salvinorin A effects (e.g., cartoon-like imagery) to other neurological conditions with overlapping phenemenology (e.g., Charles Bonnet syndrome; Ffytche et al. 1998). Together, the qualitative findings in the present study point to the need for a more diverse range of quantitative outcome measures in order to characterize the unique effects of kappa-opioid agonists. Some studies have developed novel questionnaires based on participant reports of hallucinogenic, dissociative, and opiate-like effects (Sumnall et al. 2011; Addy 2012), although validation of these measures would require large, heterogenous sample sizes. Objective measures (e.g., behavioral tasks) and novel qualitative methods for analyzing open-ended responses (e.g., audio recordings and written narratives) may also prove useful.

The inhalation methodology used in the present study appears superior to administration methods used in two past human studies of salvinorin A. Mendelson et al (2011) failed to demonstrate any effects of salvinorin A after sublingual administration. Using a different vaporization procedure than in the present study, Ranganathan et al. (2012) showed only weak effects of salvinorin A and failed to show dose-related effects comparing 8 and 12 mg. For example, on HRS Intensity, their doses of 8 and 12 mg both produced effects equivalent to about 3 μg/kg in the present study (40-60 fold difference). Given the extreme differences in potency shown across these studies, future research should exercise caution and base doses upon studies using identical inhalation methods. Finally, Addy (2012) did show reliable effects after inhalation of fortified salvinorin A plant material. While effective, that

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procedure potentially confounds salvinorin A administration with administration of other materials in the plant.

In conclusion, the present study provides novel information about the somatosensory, perceptual, cognitive, abuse liability, and qualitative subjective effects of salvinorin A, a selective kappa agonist and active constituent of an emerging and unique recreational drug, *S. divinorum*. The effects reported herein complement the large database of nonhuman studies of salvinorin A and may be relevant to understanding the neurobiology of the kappa opioid system. The overall pattern of results indicates that the effects of salvinorin A are readily manageable under laboratory conditions and there is no indication of persisting adverse effects. Given increasing interest in therapeutic applications of kappa agonists, we judge that future studies of salvinorin A can be undertaken in salvinorin A naïve participants without appreciable risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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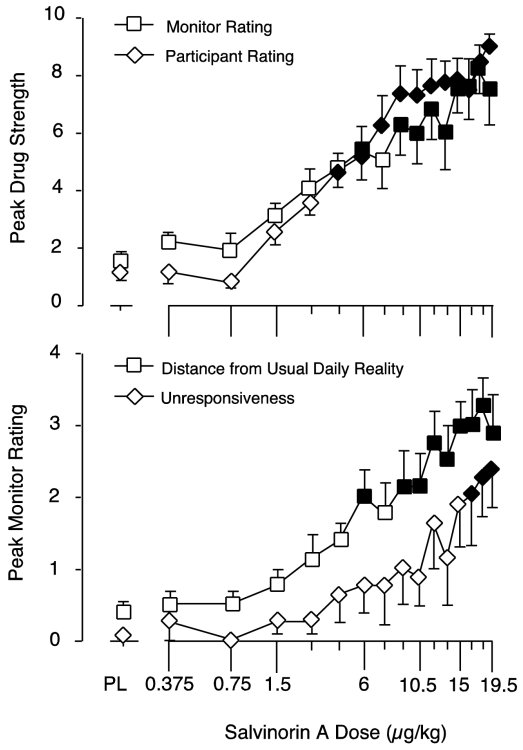


Figure 1.

Dose-related effects of Salvinorin A on Measures of Drug Strength and Dissociative Effects Participant and monitor ratings of peak drug strength (top panel); monitor ratings were converted to a 10-point scale for graphic purposes (original ratings were made on a 5-point scale). Peak monitor ratings of Unresponsiveness and Distance from Usual Daily Reality (bottom panel). Data points show mean ratings and brackets show plus or minus 1 *SEM* (*N* = 8 for all doses through 19.5 μg/kg). X-axes show dose (μg/kg) on a logarithmic scale. Filled symbols indicate that the data point was significantly different from placebo (Dunnett's pairwise comparison, $p < .05$).

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Table 1

Participant ratings on questionnaires completed at the end of each drug session

Salvinorin A dose (μg/kg)																
	Placebo	**0.375**	**0.75**	**1.5**	**3**	**4.5**	**6**	**7.5**	**9**	**10.5**	**12**	**13.5**	**15**	**16.5**	**18**	**19.5**
Single Items																
Drug Strength*	1.10	1.13	0.88	2.88	**3.63**	**4.88**	**5.38**	**5.88**	**6.13**	**6.75**	**7.5**	**6.88**	**7.63**	**6.88**	**8.13**	**8.25**
Drug Liking*	0.38	0.25	0.13	1.88	2.00	**2.50**	2.13	**3.28**	1.25	**2.25**	**2.75**	**2.25**	2.13	**2.25**	**2.38**	**2.63**
Good Effects	0.49	0.50	0.38	1.25	1.50	2.25	1.75	2.13	1.88	2.00	2.25	2.00	2.13	2.25	2.25	2.50
HRS																
Intensity*	0.58	0.63	0.59	**1.56**	**1.75**	**2.12**	**2.09**	**2.25**	**2.22**	**2.34**	**2.56**	**2.28**	**2.69**	**2.41**	**2.56**	**2.78**
Somaesthesia*	0.13	0.17	0.14	0.41	0.51	**0.87**	0.75	0.83	0.82	**0.89**	1.11	0.78	**1.20**	**0.97**	**1.03**	**1.12**
Affect*	0.54	0.67	0.5	0.79	0.85	1.08	0.87	1.17	0.92	1.08	**1.31**	1.04	**1.32**	1.11	**1.42**	**1.40**
Perception*	0.08	0.09	0.06	0.29	0.52	0.74	0.66	**0.96**	0.81	0.84	**0.94**	**0.92**	**1.07**	**0.96**	**1.08**	**1.32**
Cognition*	0.09	0.05	0.05	0.26	0.3	0.62	0.47	0.68	0.63	**0.75**	**0.93**	0.46	**1.02**	**0.96**	**1.00**	**1.01**
Volition	1.19	1.16	1.5	1.34	1.27	1.45	1.47	1.5	1.88	1.52	1.8	1.55	1.72	1.72	1.86	1.73
APZ																
OSE*	0.63	0.88	0.25	1.63	2.50	4.00	2.75	4.38	2.88	4.38	**5.13**	4.25	**5.38**	**4.88**	**5.50**	**4.88**
AIA	0.21	0.00	0.13	1.13	1.50	2.38	2.50	1.38	2.5	2.75	2.63	2.25	4.00	1.75	3.13	2.38
VUS*	0.34	0.25	0.75	0.50	0.75	2.63	2.88	2.63	2.13	2.63	3.25	2.63	**3.75**	3.13	**4.00**	3.00
M Scale																
Total*	82.1	100.6	69.9	97.8	115	139.3	117.4	139.9	136.1	142.5	161.8	148.9	158.3	151.3	**177**	**176.9**
SOCQ																
Total*	1.9	2	0.8	8	13.7	24.5	19.9	25.3	22.6	26.9	**35.8**	24.6	**35.8**	**30.8**	**40.7**	**38.2**
Unity*	0.8	0.4	0.4	5.4	14.2	25	19.2	26.7	19.2	28.3	**33.3**	20.4	**33.3**	26.7	**42.5**	**37.5**
Sacred*	0.7	1.4	0.4	8.2	11.4	23.9	19.3	26.4	23.6	29.6	**34.6**	24.3	**38.2**	28.9	**42.9**	**37.9**
Noetic	0.2	1.3	0.0	3.8	11.2	16.9	15.0	21.3	21.9	25.6	30.0	15.0	30.0	28.8	33.8	28.1
Time Space*	2.6	1.6	1.6	5.6	14.4	27.2	24.1	27.5	28.8	29.7	**43.8**	**30.6**	**41.9**	**41.9**	**44.4**	**44.1**
Positive Mood	3.5	5.4	1.4	8.6	11.8	18.9	15.4	21.4	9.6	18.9	26.4	21.1	22.9	23.2	28.9	29.6
Ineffable*	2.8	1.5	0.5	17.5	20.0	**34.5**	25.0	27.5	**34.5**	29.0	**45.5**	33.0	**48.5**	33.0	**52.0**	**50.5**
P Scale																
Total*	4.8	6.3	4.6	24.4	29.4	**51.5**	**51.0**	**48.3**	**48.6**	**55.5**	**67.9**	**52.3**	**76.0**	**67.1**	**70.5**	**68.4**
General*	1.4	1.3	1.6	6.1	5.9	10.9	10.3	10.6	10.3	11.8	**14.3**	10.1	**17.9**	**13.8**	**13.6**	**15.4**

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Salvinorin A dose (µg/kg)																
	Placebo	**0.375**	**0.75**	**1.5**	**3**	**4.5**	**6**	**7.5**	**9**	**10.5**	**12**	**13.5**	**15**	**16.5**	**18**	**19.5**
Detachment*	1.8	1.4	1.5	9.8	12.3	**21.5**	**18.8**	**21.9**	**20.8**	**22.9**	**24.8**	**20.4**	**29.6**	**23.5**	**24.6**	**25.6**
Cognitive*	1.3	1.3	0.4	5.5	6.5	12.4	10.0	11.4	11.9	**14.1**	**16.1**	12.9	**21.8**	**17.0**	**22.4**	**16.8**
Paranoia*	0.0	0.0	0.0	0.0	0.8	0.5	1.4	2.1	0.8	2.1	**3.9**	0.4	3.3	0.5	2.6	0.6
Auditory	0.1	0.4	0.0	1.4	2.5	2.0	6.5	2.6	1.9	2.8	4.5	4.5	4.0	5.8	3.1	3.9
Visual	0.3	1.1	1.1	2.1	3.1	9.6	7.6	7.4	6.6	8.0	9.1	8.9	11.0	9.9	9.0	10.1
Tactile	1.5	1.6	2.1	6.9	6.6	11.9	11.0	9.4	11.1	11.3	13.6	11.1	15.6	14.1	13.4	16.4
ARCI																
MBG	2.16	3.29	2.71	3.43	5.00	6.14	4.86	3.71	2.86	5.14	4.00	3.71	5.71	4.71	6.86	6.86
BG*	3.44	5.57	5.00	5.00	6.43	6.00	4.57	6.57	4.71	6.57	4.57	4.29	4.86	6.14	6.43	6.14
LSD	2.40	4.00	3.43	4.43	4.57	5.29	5.29	4.71	5.00	5.14	5.43	6.00	4.86	5.14	5.00	4.29
PCAG	3.30	4.43	3.43	4.71	4.14	4.14	4.29	4. 14	4.57	2.86	4.86	5.43	4.86	4.43	4.86	3.86
Amphetamine	1.68	3.14	2.14	2.71	3.86	4.00	3.00	3.00	2.71	4.43	2.71	3.29	2.71	4.00	4.29	4.00

Note. All measures were administered at the end of each session (60+ min after drug administration). Asterisks indicate that the main effect of Dose was significant ($p < .05$) for that scale or subscale. Means for Drug Disliking, Bad Effects and three P Scale subscales (Taste, Smell, Dizziness) were close to zero across all doses and are not shown. Dunnett's pairwise comparisons were conducted for each measure that showed significant effects of Dose; bold typeface indicates significantly different than placebo ($p < .05$).

Psychopharmacology (Berl). Author manuscript; available in PMC 2014 March 01.

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Table 2

Verbatim descriptions of session-day effects

Volunteer	Descriptions of Entities or Beings
S1	They are incredibly encouraging, playful, and fairy-like trickster sprites, though their personalities ranged infinitely. I saw them all move up and to the left, as I was headed in that direction: home. We were going to where I know I have always been headed and can hardly wait to experience.
S2	At the bottom of the hole was a very young being that was ready to take me and go run wild in some way … I literally felt as though one of my arms was holding onto the edge of the hole and the other arm was being pulled by the young being and I was stretching and stretching. After a bit it was as though this young being's parent established contact with me through dialogue … This being told me that when we come into their dimension it is as though we are "popping" in and that there is no control as to where this happens or who we meet … I thought to ask if there was a name for them. The being said that they are the Wonderkin.
S3	I was being taken higher and higher into another amazing realm which was occupied by a familiar nurturing (perhaps female) presence … When I arrived in the presence of this being, she made a gesture that seemed to convey the sheer absurdity of the study at hand, and the scientists themselves, for that matter. It was like a big cosmic joke that was so overwhelmingly funny that I found myself hysterically, almost uncontrollably laughing at this point.
S4	The trickster appears to my right, and a few more entities appear circling around me in all directions they are all just beyond visible sight, in the shadows. The trickster shows it self to me as Mickey Mouse.
S5	Someone else was pulling/opening this canvas at my request to reveal something, then shutting it again (like a scene collapsing on itself) … one frame is open right now, other frames around it, many active frames are always there. The fabric moves/pushes you to the background… the guy [who was pulling/opening the canvas] said 'I'll see you next year' like that's how long it would take to cycle around again. [There were] at least 1, maybe 2 distinct people in that other reality.
S6	One such plane was occupied by giant children whose looks made them appear around 12 yrs of age. They stood towering over me as I lay beneath them staring up into their faces. Then instantly I felt a great force on my entire body – pinning me down tensed in my chair. Telepathically I became aware of one of them letting me know that they were in control of my physical body and they had the power to exert certain forces over it. This was relayed to me in a somewhat playful manner, and I submitted my physical body to them in an act of subservience.
S7	After administration, I immediately felt reality shrink down to a single point, far away. The point started bouncing and became the Cheshire cat's eyes. Long-cat greeted me in salvia world and stressed the importance of proper set and setting in ensuring a pleasant salvia experience. I took this kind gesture as proof that long-cat is concerned for my mental health and well-being.
S8	At first I wasn't sure where I was until I had a realization that I was a Peep. Like the adorable little sugar crystal coated marshmallow filling molded bunnies found in an Easter basket. Not only was I a Peep but [the session monitors] were also Peeps. We were part of the same interconnected whole … I felt as though it was a sunny day, we were on a sidewalk, a little mushy but not scorched. I had the feeling that we were all waiting to be scooped off the sidewalk by a nameless, shapeless, species-less figure.
	Descriptions of Specific Autobiographical Memories
S1	I envisioned the driveway of my childhood, where I played every day. I was just grabbing my jacket from my mom in the house …This is something that I experienced in my real life uncountable times … It was simply the feelings and thoughts that go along with this event.
S4	I am around 5 years old and at a park with my parents and we came to take part in a baseball game. It was a fun game not for serious sport but mostly older people/adults were playing. Being a very shy child, when it was time for me to take a swing with a bat, it terrified me. Walking up and removing my coat exposes the shit on underneath. I am wearing a superman shirt. Everyone screams with joy and excitement! I am welcome by all! Welcome to the game, welcome to the next level!
S8	Immediately felt like a child… with this sense of having a "job" to do … We are going to hunt for chocolate Easter bunnies. This makes me very happy. I am full of joy.

Note. Each verbatim passage was chosen from a single drug session as representative of the participant's phenomenological experience of entities/beings (top) or autobiographical memories (bottom). Excerpts were chosen from participants' written narratives (composed shortly after each session) or from oral descriptions during the drug sessions (e.g., 30-60 minutes post-inhalation).