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ORIGINAL INVESTIGATION

Acute and post-acute behavioral and psychological effects of salvinorin A in humans

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Abstract
Rationale Salvia divinorum has been used for centuries, and nontraditional use in modern societies is increasing. Inebriation and aftereffects of use are poorly documented in the scientific literature.
Objectives This double-blind, placebo-controlled, randomized study analyzed subjective experiences of salvinorin A (SA) inebriation and consequences of use after 8 weeks.
Methods Thirty middle-aged, well-educated, hallucinogen-experienced participants smoked either 1,017 or 100 μg SA 2 weeks apart in counterbalanced order. Vital signs were recorded before and after inhalation. A researcher rated participants' behavior during sessions. Participants completed the Hallucinogen Rating Scale (HRS) assessing inebriation immediately after each session. Differences were analyzed between groups as functions of dose and time. After 8 weeks, participants were interviewed to determine reported consequences and aftereffects.
Results Participants talked, laughed, and moved more often on an active dose. All six HRS clusters were significantly elevated on an active dose indicating hallucinogenic experiences. No significant adverse events were observed or reported by participants.
Conclusions The present results indicate similarities as well as differences between the subjective effects of *S. divinorum* and other hallucinogens. As a selective kappa opioid receptor agonist, SA may be useful for expanding understanding of the psychopharmacology and psychology of hallucinogenic states beyond serotonergic mechanisms.

Keywords Double-blind · Hallucinogen · Hallucinogen rating scale · Human · Kappa opioid · Placebo-controlled · Psychedelic · Randomized · *Salvia divinorum* · Salvinorin A

Introduction

Salvinorin A (SA), a nonnitrogenous diterpenoid with potent and selective agonist activity at the kappa opioid receptor (KOR), is the principal psychoactive component of the Mexican mint *Salvia divinorum* (Roth et al. 2002). *S. divinorum* has been used for centuries within the Mazatec culture and others in structured manners for divinatory or religious purposes and for physical healing (Ott 1995). The psychological effects of *S. divinorum* include significant alterations in affect, behavior, and cognition (Siebert 1994) leading to "a unique profile of subjective effects having similarities to classic hallucinogens, including mystical-type experiences" (Johnson et al. 2010 p. 5). These hallucinations occur with no binding activity at the 5-HT_{2A} receptor (Roth et al. 2002), which is the principal binding site of "classic" hallucinogens. Traditionally, the leaves of the plant are chewed or brewed into a tea (Ott 1995); however, nontraditional use usually involves smoking an extract of the leaves (Baggott et al. 2010).

Four clinical studies of SA with human participants have been published. Siebert (1994) administered *S. divinorum* extracts and pure SA in an informal group

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setting of 20 participants without using double-blind randomized placebo-controlled methodology. Participants swallowed capsules of SA, absorbed an alcohol-based spray of SA on their oral mucosa, and inhaled SA vapors. Siebert determined that psychoactivity typically began at about 200 μg via vaporization. The highest dose administered via vaporization was 2,600 μg, and no acute or long-term negative effects were reported for that dose (Siebert 1994). A phenomenological account of one of participant is presented in Turner (1996). Pichini et al. (2005) focused on detection and quantification of smoked *S. divinorum* in biological fluids of two users. These first two reports provide almost no information on demographics of participants and little information on administration procedures and either behavioral or subjective effects of SA. Mendelson et al. (2010) did not obtain any psychoactive effects in eight participants, presumably due to the unreliable nature of sublingual absorption of SA. Finally, Johnson et al. (2010) completed a placebo-controlled dose–response study of inhaled SA in four participants, focusing on vital signs and objective measurements, of inebriation and briefly describing some subjective effects.

Meanwhile, human use outside of the traditional context is increasing (Wu et al. 2011). The plant is legal to buy and sell in many states and countries. In response to increased visibility of use, *S. divinorum* and SA are now scheduled in some states and have received much negative attention in the popular press (Gonzalez et al. 2006). However, little scientific research has examined either the subjective experiences facilitated by *S. divinorum* or the aftereffects of use with human participants.

SA is a potent and selective KOR agonist in vitro (Roth et al. 2002). Discrimination trials demonstrate SA to generalize to synthetic KOR agonists with both rodents (Baker et al. 2009; Wilmore-Fordham et al. 2007) and primates (Butelman et al. 2004, 2010). These generalization effects were blocked by general opioid antagonist quadazocine (Butelman et al. 2004, 2010) and KOR agonist norbinaltorphimine dihydrochloride (Wilmore-Fordham et al. 2007), were not blocked by 5-HT_2 antagonist ketanserin (Butelman et al. 2010), and were partially blocked by KOR antagonist 5′-guanidinonaltrindole (effective in two of three monkeys; Butelman et al. 2004). Further, discrimination trials demonstrate that SA does not generalize to 5-HT_2 agonists 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (Li et al. 2008), d-lysergic acid diethylamide (LSD; Killinger et al. 2010), or psilocybin (Butelman et al. 2010); CB1 agonist delta-9-tetrahydrocannabinol (Walentiny et al. 2010); delta opioid receptor agonist SNC80 (Butelman et al. 2010); mu opioid receptor agonist fentanyl (Butelman et al. 2010); or NMDA antagonist ketamine (Butelman et al. 2010; Killinger et al. 2010).

Little is known about KOR agonist activity in humans. Synthetic KOR agonists produce dysphoria and hallucinations. KOR agonist enadoline administration up to 2 μg/kg i.v. resulted in hallucinations (Walsh et al. 2001). KOR agonist MR 2034 administration of 3.8 μg/kg i.v. resulted in "somesthetic changes and disturbances in the perception of space and time....uncontrolled laughter....described their experiences as dreamlike" (Pfeiffer et al. 1986, p. 775). However, Johnson et al. (2010) noted a relative lack of dysphoric effects and significant positive effects as well as hallucinations with inhaled KOR agonist SA administered in ascending doses up to 21 μg/kg. The differences in affect between study participants may be related to any number of factors, including Johnson et al. having more stringent inclusion and exclusion criteria for participants, focusing on establishing trust and rapport with participants, and emphasizing a safe and supportive physical environment (see also Johnson et al. 2008 for a discussion of these factors).

In the present study, we used a double-blind, placebo-controlled, randomized methodology to evaluate acute (up to approximately 70 min post-inhalation) differences in observer-rated behavioral and participant-rated psychological effects of enhanced smoked *S. divinorum* leaf containing approximately 1,017 μg SA per 25 mg dried leaf relative to a placebo compound containing a presumed non-psychoactive dose (Johnson et al. 2010; Siebert 1994) of approximately 100 μg SA per 25 mg dried leaf. Participant-reported post-acute (mean, 56 days) effects were recorded as well. In contrast to the previous report of Johnson et al. (2010), the present study included 30 participants instead of four and recorded participant behavior during SA inebriation.

Materials and methods

Participants

Participants were recruited from the local community using flyers and word of mouth. Thirty-two volunteers were recruited for this study, and two dropped out after screening but before any experimental session. Inclusion criteria were: being generally physically and psychologically healthy by self-report; between the ages of 25 and 65; fluent and articulate in English (as determined in investigator interview); and willing to refrain from taking psychoactive substances, prescribed medication, and over-the-counter medication for the acute phase of the study, by self-report (mean length, 40.4 days). Exclusion criteria were admitting a history of cardiovascular or respiratory problems; a diagnosis of current or past manic episodes, psychotic symptoms, or posttraumatic stress disorder using the Structured Clinical Interview for DSM Diagnoses (SCID-I-RV/NP) (First et al. 2002) by a

trained examiner; or pregnancy by females of childbearing age. On the days when a substance was administered, an emergency medical technician (EMT) obtained a urine sample for all female participants of childbearing age to verify no participant was pregnant (Clearblue Easy Digital Pregnancy Test, Swiss Precision Diagnostic, Petit-Lancy, Switzerland).

Additionally, participants needed to have a history of using a hallucinogen one time. For the purposes of this study the term *hallucinogen* was used to describe the following chemicals: psilocybin, LSD (d-lysergic acid diethylamide), mescaline (sourced from *Lophophora williamsii* or *Echinopsis pachanoi*), ayahuasca (*N*,*N*-dimethyltryptamine [DMT] made orally active in combination with reversible monoamine oxidase inhibitors), or inhaled DMT.

Study design

The Research Ethics Committee of the Institute of Transpersonal Psychology in Palo Alto, CA, approved the study, and all volunteers gave their informed consent before participation. During the experimental sessions when a substance was administered, an EMT was present to monitor vital signs and respond to any emergency situation (no emergency situations occurred).

This double-blind, within-group, crossover study involved two sessions conducted at 2-week intervals. Thirty participants were randomly assigned to receive either the active dose or the placebo dose in the first session, with the other dosage administered in the second session. Outcome measures obtained at baseline and mean 70 min after inhalation included blood pressure, temperature, pulse rate, and respiration rate. It was determined that vital signs would not be measured while participants were inebriated as the procedures would be distracting and intrusive to the participants. No significant cardiovascular effects were noted in the previous studies of Mowry et al. (2003) on rodents or Johnson et al. (2010) on human participants. During the session, the researcher completed the Monitor Rating Questionnaire (MRQ) (available as online resource) to record participant behavior. Semi-structured interview began 30 min post-inhalation unless participants began talking sooner. At the end of the interview, the EMT recorded vital signs a second time. Finally, participants filled out the Hallucinogen Rating Scale (HRS) (Strassman et al. 1994), which was designed to assess the subjective experience of the participant.

Approximately 8 weeks after the second session, participants met with the researcher for a semi-structured open-ended interview lasting approximately 30 min. Participants were asked about perceived experiences and effects of both sessions, as debriefing occurred after this final interview. Participants were asked if they had any persisting effects after each session, whether they had sought professional help for these effects, whether they experienced any symptoms of hallucinogen persisting perception disorder (American Psychiatric Association 2000), whether their patterns of substance use changed, and whether or not they would consider using *S. divinorum* again.

Drug conditions

The *S. divinorum* was self-administered by the participant. The researcher placed 25 mg of plant material into a metal smoking pipe. The participant then ignited the material using a disposable butane lighter and inhaled the smoke. Participants were instructed to hold the smoke in their lungs for 15 s if possible. The doses were: an active dose of 1,017 μg SA dissolved onto 25 mg dried *S. divinorum* leaf and a presumed non-psychoactive placebo dose of 25 mg un-enhanced dried *S. divinorum* leaf containing approximately 100 μg SA.

The current dosage of 1,017 μg was chosen as it is known to produce reliable effects and is not known to produce significant adverse reactions. Siebert has written that 1,000 μg "is sufficient for 1–2 uses for a person of average sensitivity" (Siebert 2011). A more recent experiment (Johnson et al. 2010) used a high dose of 21 μg/kg, or approximately 1,391 μg, of pure SA inhaled by four participants.

The active doses of SA were provided and individually packaged by Mr. Siebert (*Salvia divinorum* Research and Information Center [SdRIC], Malibu, CA). This extract is sold as "Extra-Strength Standardized Salvinorin A Enhanced Leaf" (Siebert 2011). SA was extracted from *S. divinorum* and purified using a process of solvent partitioning followed by repeated recrystallization. HPLC analysis indicated 98% purity, with the main impurity being salvinorin B. One gram of 98% pure SA was dissolved in methylene chloride and mixed with 25.6 g dried *S. divinorum* leaves containing 0.4% SA (by weight), resulting in 26.6 g plant material containing 1,082.4 μg SA. This mixture was divided into 1,064 units, each theoretically containing 25 mg *S. divinorum* leaf and 1,017 μg SA. This final potency was calculated from initial conditions; it was not measured after production. Mr. Siebert states that "it is safe to say that the dosage is accurate within a plus or minus 2% margin" (D. Siebert, personal communication, February 24, 2011).

Unaltered *S. divinorum* leaf was also purchased from the SdRIC as "Sierra Mazateca Prime Harvest Dried Salvia divinorum Leaves," which the researcher then ground, measured, and packaged into identical 25-mg doses. These placebo doses theoretically contained approximately 0.4% SA, or 100 μg per 25-mg dose (D. Siebert, personal communication, February 24, 2011).

Experimental sessions

The researcher met with each participant once before the first experimental session to complete screening procedures and build rapport. During this meeting, the participant's history of hallucinogen use and mental health were reviewed.

The participant and the researcher talked about the participant's day and expectations for the session. The researcher used a progressive relaxation script and classical music (Gorecki 1976) played at low volume to help standardize the environment across sessions and to provide psychological support. The EMT was in an adjacent room for the entire session. The participant was encouraged to recline in a chair, close his or her eyes, and focus attention on inner experiences. In the event that the participant experienced fear or anxiety, he or she was encouraged to ask for assistance or put out his or her hand for the researcher to hold. All sessions were audiotaped.

Expectancy and blinding

Expectation effects were dealt with in an ethical manner as recommended in clinical hallucinogen research by Johnson and colleagues (Johnson et al. 2008). Participants were informed that they would receive two different dosages. Each could be anywhere between 0 and 1,500 μg SA (in reality, there were only two dose conditions: 100 and 1,017 μg). This was done so that participants could expect a psychoactive dose for each session and reduce the placebo effect and other expectation-related effects. After the follow-up interview was complete, this deception was revealed. All 30 participants correctly identified the active and placebo conditions once asked.

To ensure the researcher was blind as well, each pair of doses was sealed in individual envelopes. At the beginning of each session, the researcher picked one dose at random, saving the second dose for the second session. A one-sample t test suggested that neither condition sequence was more likely: $t(29)=0.724$, $p=0.475$.

Physiological measures

Approximately 10 min before and 60 min after inhalation, the EMT recorded blood pressure and heart rate using oscillometric method with the blood pressure cuff placed on the wrist (TV3649, North American Healthcare). Temperature was measured using a digital oral thermometer (KD-153, Bestmed, Golden, CO). Respiration rate was measured visually over a period of 30 s.

Behavioral and psychological measures

During the experimental session, the researcher filled out the MRQ, which was created by the researcher and comprised 19 descriptions of observable behavior in the participant. These descriptions were taken from the survey of Baggott et al. (2010) and the DSM criteria for opioid intoxication (American Psychiatric Association 2000). These behaviors were recorded in one of two ways. First, for each 10-min interval, 14 behaviors were rated on a scale of 0–10 based upon the number of minutes during which the participant engaged in the behavior (runny nose, sneezing, vomiting, eyes open, eyes closed, watery eyes, talking, laughing, non-speech noises, statements relating to paranoia, yawning, movement while sitting, movement while standing, and physical contact with a monitor). Second, five behaviors were marked as either observed or not observed during each 10-min period (dilated pupils, goose bumps, sweating, lack of coordination, and unresponsiveness). This allowed for quantitative assessment of the behavioral effects of SA inebriation. MRQ scores between 0 and 20 min post-inhalation were analyzed, as Johnson et al. (2010) suggested that "by 20 min after inhalation, mean ratings indicated only a 'possible mild' effect" (p. 3) and Siebert (1994) suggested that "the strongest effects last 5–10 min and then gradually subside over about 20–30 min" (p.55).

Sixty minutes after inhalation, the HRS was completed by the participant. This 126-item questionnaire was designed to assess the psychoactive effects of DMT and has since been used to measure the effects of other hallucinogens, including ayahuasca (Riba et al. 2004), ketamine (Lofwall et al. 2006), MDMA (Tancer and Johanson 2007), psilocybin (Griffiths et al. 2006), and SA (Johnson et al. 2010). The scale is composed of six clusters which can range from 0 to 4 measuring various aspects of the subjective experience of hallucinogen use:

> (1) Somaesthesia—interoceptive, visceral, and cutaneous/tactile effects; (2) Affect—emotional/affective responses; (3) Perception—visual, auditory, gustatory, and olfactory experiences; (4) Cognition—alterations in thought processes or content; (5) Volition—a change in capacity to willfully interact with themselves, the environment, or certain aspects of the experience; and (6) Intensity—strength of the various aspects of the experience. (Strassman et al. 1994)

Data analyses

Missing data on the HRS were not averaged when creating cluster scores. Quantitative analyses were performed using SPSS v16 (IBM, Armonk, NY). Effect sizes (r) were calculated using the formula published by Hinton (2004). All data were analyzed for normality using a one-sample Kolmogorov–Smirnov test. Normally distributed data were subjected to two 2-way ANOVAs: a 2×2 (time [pre, post]×

dose [active, placebo]) repeated measures ANOVA compared vital signs, and a 2×2 (sex [female, male]×dose [active, placebo]) mixed measures ANOVA compared vital signs pre-inhalation, vital signs post-inhalation, MRQ scores, and HRS cluster scores. Non-normally distributed data were analyzed using Wilcoxon Signed Rank tests to assess effects of time and dose and Mann–Whitney *U* tests to assess effects of sex. Significant tests and results are discussed below. Sex did not show any significant main effects or interactions with dose or time on any outcome measure.

Results

Demographics are presented in Table 1.

Physiological measures before and after sessions

Diastolic blood pressure and pulse rate declined across the session independently of dose (time, $F(1,29)=4.801$, $p=0.027$, $r=0.38$ and pulse rate, $F(1, 29)=9.045$, $p=0.006$, $r=0.49$). Diastolic blood pressure dropped an average of 4.2 mmHg between measurement times, and pulse rate dropped an average of 5.2 bpm between measurement times. No significant differences were noted as a function of time or dose on temperature or systolic blood pressure. Respiration rate was slightly higher on the active session, but it was higher even before the SA was inhaled. Vital sign statistics and comparison by dose condition are shown in Table 2.

Behavioral effects during session

No participant was observed sneezing, vomiting, having goose bumps, or being unresponsive. Five variables were normally distributed for both dose conditions: eyes open, eyes closed, talking, laughing, and movement while sitting. SA inhalation increased talking, laughing, and movement while sitting: talking $F(1,28)=4.306$, $p=0.047$, $r=0.37$; laughing $F(1,28)=14.774$, $p=0.001$, $r=0.59$; movement while sitting $F(1,28)=12.761$, $p=0.001$, $r=0.56$. A participant displayed 11.6 instances of talking with an active dose and 9.9 instances with a placebo dose, displayed an average of 3.9 instances of laughing with an active dose and 1.2 instances with a placebo dose, and displayed 8.8 instances of moving while in their chair with an active dose and 4.9 instances with a placebo dose.

The drug also increased physical contact with the monitor (Wilcoxon Signed Rank Test; $z=-2.724$, $p=0.006$) and paranoid ideation ($z=-2.333$, $p=0.02$; Table 3). During pre-inhalation preparation, participants were encouraged to ask to hold hands with the researcher if he or she felt anxious,

Table 1 Demographic characteristics of participants

	Participants ($n=30$)
Age	
Mean [range], years	39 [25–65]
Female, *n* (%)	14 (47)
Marital status, *n* (%)	
Single	19 (63)
Married	7 (23)
Divorced or annulled	4 (13)
Have children	6 (20)
Education, *n* (%)	
Some college	7 (23)
College graduate	13 (43)
Post-graduate	10 (33)
Number of alcoholic drinks in past month, *n* (%)	
0	8 (27)
1–7	9 (30)
10–14	5 (17)
24–26	4 (13)
36	2 (7)
60	1 (3)
180	1 (3)
Number of times smoked marijuana in past month, *n* (%)	
0	16 (53)
1–6	2 (7)
20	1 (3)
30	1 (3)
90	1 (3)
105	1 (3)
Previously used psychedelic substances	
Psilocybin	25 (83)
LSD[a]	21 (70)
Salvia divinorum	11 (37)
MDMA[b]	15 (50)
Mescaline	10 (33)
Ayahuasca	9 (30)
DMT[c]	4 (13)
Ketamine	3 (10)
Ibogaine	2 (7)
LSA[d]	2 (7)
Amanita muscaria	2 (7)
DXM[e]	2 (7)
2-CB or 2-CE[f]	2 (7)
5-MeO-DMT[g]	2 (7)

[a] d-Lysergic acid diethylamide

[b] 3,4-Methylenedioxymethamphetamine

[c] *N*,*N*-Dimethyltryptamine

[d] d-Lysergic acid amide

[e] Dextromethorphan

[f] 4-Bromo-2,5-dimethoxyphenethylamine or 2,5-dimethoxy-4-ethylphenethylamine

[g] 5-Methoxy-*N*,*N*-dimethyltryptamine

Table 2 Comparison by dose condition of physiological measures of participants during the session

Variable	Placebo		Active		*F* value[a]	*P* value
	Before	After	Before	After		
Respiration	16[b] (3)	16[b] (2.3)	17[b] (2.7)	17[b] (3.2)	−2.523[c]	0.012*
Systolic	129.1 (16.8)	125.3 (12.9)	130.4 (15.8)	132 (17.5)	3.711	0.064
Diastolic	79.1 (12.5)	75.1 (9.4)	81.7 (12.4)	77.1 (12.2)	1.946	0.174
Pulse	71.6 (11.8)	64.1 (13)	71.2 (13.9)	68.3 (12.5)	1.164	0.290
Temperature	97.1 (1.1)	97.3 (0.8)	97.4 (0.7)	97.1 (0.9)	0.443	0.511

Data are mean scores with one standard deviation shown in parentheses (n=30)

*p<0.05

[a] df=1,28

[b] Median used instead of mean for nonparametric data

[c] Nonparametric data were analyzed using Wilcoxon Signed Rank Test

confused, or overwhelmed during the experience. Participants later described the experience of physical contact as "grounding" and "stable." Participant verbalizations that were deemed indicative of paranoid ideation included "I'll bet I sound crazy, don't I?"

Post-session account of experience

Five of the six HRS clusters were normally distributed and analyzed by ANOVA. The intensity cluster was not normally distributed and was analyzed using the Wilcoxon Signed Rank Test. The active dose condition increased ratings on all six HRS cluster scores: affect, cognition, intensity, perception, somaesthesia, and volition (see Table 4).

In addition, all participants were asked to compare their experience with *S. divinorum* to other altered states of consciousness. The following percentage of participants reported their experience was similar in part to that of dreaming (43%), LSD (13%), psilocybin (10%), marijuana (10%), MDMA (10%), non-substance-facilitated altered states of consciousness such as meditation, trance and yoga (7%), or NMDA antagonists such as dextromethorphan (DXM) and ketamine (7%). Fifty percent of participants remarked that their experience was unlike any previous experience of an altered state of consciousness.

8-week follow-up

Follow-up interviews were conducted an average of 56 days after the second experimental session. Interviews were conducted with all 30 participants; however, seven recordings were lost due to technical difficulties. All percentages are based on remaining records (n=23). It should be noted that

Table 3 Monitor ratings of participant behavior throughout the session

Behavior	Placebo	Active	*F* value[a]	*P* value
Movement while sitting	4.9 (2.8)	8.8 (5.3)	12.76	0.001*
Laughing	1.2 (1.3)	3.9 (4.3)	14.77	0.001*
Physical Contact	0	0.5[b] (0.8)	−2.724[c]	0.006*
Paranoia	0	0.2[b] (0.5)	−2.333[c]	0.020*
Talking	9.9 (4.1)	11.6 (4.9)	4.31	0.047*
Sweating	0[b] (0.2)	0.2[b] (0.5)	−1.89[c]	0.059
Uncoordination	0	0.1[b] (0.3)	−1.414[c]	0.157
Watery eyes	0	0.2[b] (0.9)	−1.342[c]	0.180
Dilated pupils	0	0.3[b] (1.3)	−1.342[c]	0.180
Non-speech noises	0.6[b] (0.9)	1[b] (1.2)	−1.313[c]	0.189
Runny nose	0.1[b] (0.4)	0[b] (0.2)	−1[c]	0.317
Eyes closed	7.9 (6)	6.8 (5.7)	0.9	0.352
Yawning	0.2[b] (0.8)	0.3[b] (1.2)	−0.816[c]	0.410
Eyes open	12.1 (5.7)	12.8 (5.7)	0.4	0.533
Movement while standing	0.4[b] (1.8)	0.4[b] (1.2)	−0.53[c]	0.596

Data are mean minutes participants engaged in behavior with one standard deviation shown in parentheses (n=30)

*p<0.05

[a] df=1,28

[b] Median used instead of mean for nonparametric data

[c] Nonparametric data were analyzed using Wilcoxon Signed Rank Test

Table 4 Participant ratings on Hallucinogen Rating Scale completed 1 h after drug administration

Cluster	Placebo	Active	*F* value[a]	*P* value
Affect	0.75 (0.47)	1.5 (0.58)	35.157	<0.001*
Cognition	0.37 (0.41)	1.61 (0.81)	71.177	<0.001*
Intensity	0.38[b] (0.76)	3[b] (0.77)	−4.786[c]	<0.001*
Perception	0.33 (0.36)	1.71 (0.73)	95.285	<0.001*
Somaesthesia	0.31 (0.33)	1.27 (0.54)	72.043	<0.001*
Volition	0.94 (0.53)	1.85 (0.46)	55.562	<0.001*

Data are mean ratings with one standard deviation shown in parentheses (n=30)

*p<0.05

[a] df=1,28

[b] Median used instead of mean for nonparametric data

[c] Nonparametric data were analyzed using Wilcoxon Signed Rank Test

participants not noting an effect does not ensure the absence of such effect.

Twenty participants (87%) reported aftereffects lasting less than 24 h after smoking (Table 5). Positive effects were more commonly reported than negative effects: there were 18 reports of positive aftereffects (reflection, empathy, intuition, aware of beauty) and nine reports of negative aftereffects (headache, fatigue, difficulty concentrating).

Sixteen participants (70%) reported aftereffects lasting more than 24 h after smoking (see Table 6). Three people reported negative aftereffects: a headache persisting for 3 days, feeling "a little bit unsure of things," and being impatient and having a labile affect. During the follow-up interview, 20 participants (87%) stated they would like to use *S. divinorum* again. Three people (13%) did not know if they would ever use the plant again, but they were not essentially opposed to the idea. No participant said they would not use again.

Table 5 Participants reporting effects lasting less than 24 h

Number	Percent	Effect
20	87	Total
5	22	Reflective, curious
5	22	More emotionally sensitive or empathic
4	17	General positive aftereffects (e.g., awe of reality; laughter; euphoric, antidepressant; calm, relaxed, peaceful, happy)
3	13	Headache
3	13	Fatigue
3	13	Difficulty concentrating
2	9	More intuitive (e.g., with self, with clients)
2	9	Feelings of floating or lightness
2	9	More aware of beauty

n=23

Discussion

This study was the first to objectively assess behaviors of participants during inebriation in a controlled setting, as well as record self-reports during an 8-week follow-up. This is the second controlled study to characterize acute psychoactive effects of SA in humans as compared to a placebo substance, with the present study using a greater number of participants than the previous work of Johnson et al. (2010). This study has face validity and generalizability to the general population due to recreating the typical route of administration by smoking an extract of *S. divinorum*. Consistent with previous human (Johnson et al. 2010) and rodent (Mowry et al. 2003) research, no significant changes in heart rate or blood pressure were observed during the controlled administration of SA. Healthy, hallucinogen-experienced participants tolerated both doses.

Behavioral analysis

The MRQ was designed to record direct observations of the effects of *S. divinorum*. In a recent uncontrolled analysis, Lange et al. (2010) created an instrument to analyze observable effects of *S. divinorum* inebriation based on 34 videos from YouTube of people smoking what was claimed to be *S. divinorum*. They used a 42-item checklist partially based on the HRS, resulting in five categories: "(1) hypo-movement, (2) hyper-movement, (3) emotional effects included being visibly excited or afraid, (4) speech effects and finally (5) heating effects related to being hot or heated" (Lange et al. 2010 p. 139).

Four of these five themes were confirmed in the present study using both objective (MRQ) and subjective (HRS, interviews) measures. No hypo-movement was observed, likely because all participants were reclining and relaxed before inhaling *S. divinorum* as part of the controlled conditions for safety reasons. However, participants were observed laughing and moving more often, and they were also visibly afraid as evidenced by statements such as "I had the fear." Although they had difficulty speaking or later described difficulty speaking, these speech effects were not statistically significant. Finally, participants described being hot in the present study. Direct comparison with the Lange et al. (2010) reports is tentative because of differences in set, setting, and dosage. As shown by Wolowich et al. (2006) and Tsujikawa et al. (2008), commercial products labeled as *S. divinorum* extract may be of unknown potency and purity.

Analysis of experience

There is much overlap between the results of the present study and those of Johnson et al.'s (2010) study also utilizing the HRS to measure inhaled SA inebriation. Johnson

Table 6 Participants reporting effects lasting more than 24 h

Number	Percent	Effect
16	70	Total
5	22	Positive changes in relationships with living family members
5	22	Reflecting on and integrating their experience
4	17	General positive changes in themselves (e.g., general sense of well-being; aligned with the stars and wholesome feelings; more grounded, present; calming, focusing)
3	13	Negative effects (e.g., headache for 3 days; unsure of things; ears popping, ready to cry, lack of patience)
2	13	Increased empathy or sensitivity (with children, with intimate partner)
2	13	Receiving lessons (e.g., about intimate partner, about working with psychotic clients)
2	9	Positive changes in relationships with others (e.g., deceased mother, a saint)

n=23

et al. administered vaporized SA to four healthy, hallucinogen-experienced participants. Johnson et al. adjusted doses by body weight, while the present study used absolute doses of 100 and 1,017 μg SA. The average participant weight for Johnson et al. was 66.15 kg, which makes the present study's doses equivalent to 1.5 and 15.4 μg/kg, respectively. There are similarities when comparing HRS cluster scores between studies. Doses of 1.5 μg/kg produced no psychoactive effects for either research group. The dose of 15.4 μg/kg shows more variability. At that dosage, Johnson et al. (2010) reported three of six clusters to be significantly different from placebo (cognition, intensity, and somaesthesia), while in the current study, all six clusters were significantly elevated.

Differences between participants and experimental conditions make it difficult to compare HRS scores or subjective ratings across studies. Nevertheless, the current study using inhaled enhanced *S. divinorum* leaf found HRS scores similar to intravenous ketamine on ratings of affect (Gouzoulis-Mayfrank et al. 2005), cognition (Gouzoulis-Mayfrank et al. 2005), perception (Bowdle et al. 1998; Krupitsky et al. 2002), and somaesthesia (Gouzoulis-Mayfrank et al. 2005) clusters. Intensity and volition clusters were similar to intravenous DMT (Strassman et al. 1994). Five of the eight substances examined with the HRS were taken orally: amphetamine (Barbanoj et al. 2008), ayahuasca (Riba et al. 2001), MDMA (Tancer and Johanson 2007), methylphenidate (Griffiths et al. 2006), and psilocybin (Griffiths et al. 2006). Orally active substances showed few similarities to inhaled *S. divinorum* or SA, while intravenously injected substances showed greater similarities to SA. Therefore, these tentative similarities may be due to the route of administration more than to neurochemical effects.

Several previous studies have identified themes in the participant narratives regarding the SA effect. Participants in this study indicated six of the seven "themes" reported by Siebert (1994): a sense of "becoming objects; visions of various two-dimensional surfaces, films and membranes; loss of the body and/or identity; various sensations of motion, or being pulled or twisted by forces of some kind; uncontrollable hysterical laughter; and overlapping realities" (p. 55). The only theme Siebert reported that this study did not confirm was of "revisiting places from the past, especially childhood" (p. 55). Johnson et al. (2010) reported five common "themes" across participant narratives given various doses of salvinorin A up to 21 μg/kg: "changes in spatial orientation, feelings of energy or pressure on different parts of the body…revisiting childhood memories, cartoon-like imagery and contact with entities" (p. 5). Four of these themes were described by participants in the current study, again with the exception of revisiting childhood memories. Neither Siebert nor Johnson et al. mentioned utilizing a rigorous methodology to elucidate themes, and participants' not noting an effect does not ensure the absence of such effect. Still, there appears to be some amount of overlap between experiences reported in these three studies.

Limitations

The study had several limitations. Vital sign observations were made an average of 70 min apart, while subjective effects lasted approximately 20 min post-inhalation; therefore, physiological reactions to inhaled SA may have resolved before measurement. The use of the smoked route increased the generalizability of the results as this is the most common route of administration for the general population (Baggott et al. 2010; Gonzalez et al. 2006). However, the findings may not apply to other routes of administration, including sublingual (Mendelson et al. 2010; Siebert 1994). The dose of SA delivered by smoking may have varied between participants, and quantitative assays of the prepared material were not conducted. Some SA may have decomposed during burning. Participants were allowed to self-administer, leading to idiosyncratic smoking behavior such as time spent inhaling and time spent between inhalation and exhalation.

Another limitation is that the aftereffects were based on self-report; no quantitative measures were used. Other possible concerns were the crossover design and the 8-week limit on the follow-up interview: longer wait time before follow-up may have yielded different results. Finally, there are limitations to the outcome measures. Self-report measures are subject to bias and selective memory, and the MRQ is subject to expectation effects on the part of the researcher. Nevertheless, the quantitative self-report, quantitative researcher observation, and qualitative interview used here were designed to minimize the limitations of relying on only one of these sources of data.

Conclusions

S. divinorum contains a potent psychoactive which facilitates hallucinogenic states of consciousness under controlled conditions. Using safe and ethical research procedures (Johnson et al. 2010; Mendelson et al. 2010; Pichini et al. 2005; Siebert 1994), the immediate and lasting effects of SA can be assessed.

S. divinorum occasions hallucinogenic and mystical-type experiences (Johnson et al. 2010), but does not bind to the 5-HT_2 receptor (Roth et al. 2002) as do "classic" hallucinogens. *S. divinorum*, as demonstrated in this study, is of clear interest to psychology as well as to psychopharmacology and the study of hallucinogenic states of consciousness beyond serotonergic mechanisms.

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