

# **A Literature Review on the Status and Effects of Salvia Divinorum on Cognitive, Affective, and Behavioral Functioning**

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Boca Raton

*A Literature Review on the Status and Effects of Salvia Divinorum on  
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**Abstract**

Salvia divinorum is a hallucinogenic herb that was originally used in the Mazatec Indian culture of Oaxaca, Mexico for spiritual and medicinal purposes (Wasson, 1962). Salvia divinorum produces powerful hallucinogenic effects when the leaves are chewed, orally consumed in a liquid state, or dried and smoked. Its active ingredient is Salvinorin-A (Roth et al., 2002; Siebert, 1994), a highly selective kappa ( $\kappa$ )-opioid receptor agonist (Roth et al., 2002), that researchers consider to be the most potent naturally occurring hallucinogen (Ortega, Blount & Manchand, 1982; Siebert, 1994; Valdes et al., 1984). In recent years, the use of Salvia divinorum as a recreational drug has become increasingly popular (Vortherms & Roth, 2006), facilitated by the availability of the drug and videos (e.g., YouTube) documenting its hallucinogenic effects on the internet (Gonzalez, Riba, Bouso, Gomez-Jarabo, & Barbanoj, 2006). The purpose of the current clinical research project is to critically review the literature to investigate the effects Salvia divinorum use has on cognitive, affective, and behavioral functioning in humans. The review has implications for research on depression, anxiety, addiction, Parkinson's disease, and Alzheimer's disease. The study also provides a review of DSM-IV-TR diagnoses and precautions in diagnosing for clinicians. Based on this review, recommendations are provided in areas for future research, development of assessment instruments, and areas requiring clinical attention. Furthermore, the current study will act as a comprehensive review of the history, background, and research of Salvia divinorum for the use in future studies and for the purpose of educating clinicians and the general public about the substance.

## Chapter 1

### History and Background

#### *Introduction*

Salvia divinorum is one of more than 700 members of the plant genus “salvia,” and is considered a member of the sage and mint family (Valdes & Seymour, 1998). Salvia divinorum was primarily used by the Mazatec Indian culture of Oaxaca, Mexico for medicinal and spiritual purposes (Wasson, 1962). Medicinal uses include treatment of diarrhea and headaches (Valdes, Diaz, & Paul, 1983). However, the plant also possesses psychoactive properties that induce powerful hallucinations that are useful in spiritual and religious rituals (Wasson, 1962). Salvia divinorum is generally used by (a) chewing the leaves, (b) drinking juice made from crushing the leaves, or (c) smoking dried leaves or extracts (Siebert, 1994). In recent years, Salvia divinorum has become an increasingly popular recreational drug (Vortherms & Roth, 2006), facilitated by its availability on the internet, as well as information on how to use it and videos (e.g., YouTube) documenting its hallucinogenic effects (Gonzalez, Riba, Bouso, Gomez-Jarabo, & Barbanoj, 2006). Salvia divinorum tends to be attractive to adolescents because it is often marketed as an alternative to marijuana and advertised as being highly safe. It is also easy to obtain and legal in most states. However, despite an increase in Salvia divinorum research over the last 20 years, little is known about the short- and long-term effects on an individual’s cognitive, affective, and behavioral functioning. Some studies have found Salvia divinorum to have therapeutic properties, but other studies have failed to replicate these findings. In the first chapter, the author will provide an in-depth description of the definition of Salvia divinorum. The focus will be to inform the reader about the herb’s history, pharmacology, status in the world, and prevalence.

## ***Background***

Salvia divinorum is an herb in the Labiatae, or mint family, and is native to certain areas in the Sierra Mazateca of Mexico (Epling & Játiva-M, 1962). The plant grows to well over one meter in height and consists of large green leaves, hollow square stems, and has white flowers with purple calyces (Valdes, Díaz & Paul, 1983). The sage is found in forest ravines and other moist or humid areas of the Sierra Mazateca.

There are a number of common names for Salvia divinorum and many are related to the herb's association with the Virgin Mary (Valdes, Díaz & Paul, 1983; Wasson, 1962). The Mazatecs refer to Salvia divinorum as *hojas de la Pastora*, or *hojas de María Pastora* ("leaves of the Shepherdess" or "leaves of Mary the Shepherdess"), and may also be known as "*ska pastora*" or "*ska Maria pastoria*." The Mazatecs believe Salvia divinorum is the incarnation of the Virgin Mary, and a great deal of care is taken not to damage the plant when picking the leaves. Other common street names include "Diviners Sage," "Mystic Sage," and "Magic Mint" (Babu, McCurdy & Boyer, 2008).

R. Gordon Wasson was the first to publicize Salvia divinorum, in 1953, based on his work studying the role of mushrooms in the religious life of the Mazatecs. The Mazatecs used several hallucinogenic plants in their religious rituals (i.e., Salvia divinorum, psilocybin mushrooms, peyote, and morning glory seeds containing lysergic acid amide). The Mazatecs used Salvia divinorum when mushrooms were scarce. Wasson carefully documented how the plant was prepared and used in religious rituals. He also records his own experience with the drug:

"The effect of the leaves came sooner than would have been the case with the mushrooms, was less sweeping, and lasted a shorter time. There was not the slightest doubt about the effect, but it did not go beyond the initial effect of the mushrooms-

dancing colors in elaborate, three-dimensional designs. Whether a larger dose would have produced a greater effect, I do not know” (Wasson, 1962).

In 1962, Wasson gave the first specimens of the plant to Carl Epling at the University of California (Siebert, 1994; Wasson, 1962), at which point it was formally named and classified.

### ***Psychoactive Effects***

As mentioned, *Salvia divinorum* produces powerful hallucinogenic effects when the leaves are chewed, orally consumed, or dried and smoked. When smoked, the hallucinogenic effects occur quite rapidly and often within seconds of inhalation. The onset of the effects after chewing fresh leaves takes longer due to the slower rate of absorption, but still may be felt as early as five minutes after ingestion. Despite the powerful nature of *Salvia divinorum*, the hallucinatory effects are short-lasting and often peak and reside within three to ten minutes after smoking the leaves.

The psychoactive effects are largely subjective which make them difficult to study. The effects are said to be highly dose-dependent with larger doses causing extreme hallucinatory experiences (Lange, Reed, Ketchie-Croff, & Clapp, 2008). Siebert (1994) concluded the psychoactive effects experienced by *Salvia divinorum* users depends on factors such as dosage, set, and setting. He found that people frequently report visual hallucinations; and with higher dosages may experience out of body sensations. In addition, reports of depersonalization, transforming into objects, traveling into the past or other dimensions, flying through space, and laughter have all been commonly reported by those who have used the substance. Furthermore, “bad trips” have been reported by those who experienced hallucinations, and it is speculated these experiences may be related to the dosage as well as environmental influences.

### ***Traditional Uses***

As previously mentioned, *Salvia divinorum* was used by shamans for medicinal, ritualistic, and divination purposes. The plant species known as “salvia” is used for medicinal purposes in cultures throughout the world, and the name itself comes from the Latin word “salvare,” which means “to save.” Unlike Western cultures, Mazatec medicine and religion are united in the treatment of illnesses. Mazatecs are nominally Catholic Christians who incorporated many features of their traditional beliefs into conceptions of God, the Virgin Mary, and Saints, whom they view as being healers (Valdes, Díaz & Paul, 1983).

Shamans used *Salvia divinorum* to induce hallucinations for several spiritual and medicinal purposes. One such purpose would be when an individual suffers from an unknown illness and the herb is used to aid in diagnosis (Kapit, 2003). The shaman will gather the leaves while praying and then create an infusion with the fresh leaves of the plant. At midnight the curandero, or “shaman healer,” along with the patient and a witness will go to a dark place where the patient will ingest the solution. The patient will then enter into a semi-delirious trance and the curandero will make a diagnosis based on the patient’s speech. The session will end by bathing the patient in a portion of the infusion and the next morning the patient will have been cured of the illness (Kapit, 2003; Valdes, Díaz & Paul, 1983; Weitlaner, 1952).

*Salvia divinorum* is also used for shamanic training or apprenticeship into becoming a healer. Psychotropic plants are closely associated with the training, which can last several years. The Mazatecs believe the herb allows them to become acquainted with the “way to heaven,” where they are taught by visions, and may speak with the Virgin Mary, God, and Saints. Through the visions, and under the supervision of the master who also consumes the plant with the apprentice, the apprentice learns the ways of healing and the knowledge of medicinal plants by

visiting a tree in Heaven that possesses all of the herbs. *Salvia divinorum* is also used to foretell the future and obtain answers to questions about friends, family, or enemies (Valdes, Díaz & Paul, 1983).

*Salvia divinorum* has also been used by curanderos to help find lost objects or animals, along with helping victims of crimes identify their perpetrator. The shaman will administer a dose of prepared *Salvia divinorum* to the person and then listens carefully as they speak. It is believed the person will tell the shaman the location of the lost object or discuss the crime committed (Kapit, 2003).

According to Valdes and colleagues (1983), *Salvia divinorum* is not just used for the psychoactive or hallucinatory effects in the Mazatec culture. It is also a common practice for healers to administer small doses of *Salvia divinorum* to treat various ailments, such as providing relief from headaches, rheumatism, and diarrhea. It is believed that *Salvia divinorum* can help alleviate pain related to headaches and rheumatism; however, according to cuarenderos high doses that induce visions may leave one with a headache the following day. Shamans also believe that small doses of the herb can help one to defecate or eliminate diarrhea. Furthermore, there is a “semi-magical” disease known as panzon de barro, or swollen belly, which is caused by an evil sorcerer. The disease consists of the victim’s swollen midsection which is due to a “stone” put inside of the individual by the sorcerer. *Salvia divinorum* is thought to eliminate the “stone” and will result in the stomach shrinking down to normal size (Valdes, Díaz & Paul, 1983).

### ***Pharmacology/Chemistry***

*Salvia divinorum* owes its psychoactive properties to salvinorin-A, which is the main active principle of the herb (Roth et al., 2002; Siebert, 1994). Salvinorin-A is a non-nitrogenous

neoclerodane diterpene and is thought to be the most potent naturally occurring hallucinogen (Ortega, Blount & Manchand, 1982; Siebert, 1994; Valdes et al., 1984). Salvinorin-A is a potent and highly selective kappa ( $\kappa$ )-opioid receptor agonist and is considered the first nonalkaloid opioid subtype-selective substance (Roth et al., 2002). Furthermore, salvinorin-A does not show affinity to the  $\mu$ - or  $\delta$ -opioid receptors (Wang et al., 2005). *Salvia divinorum*'s unique chemical structure and qualities are unlike that of other classic hallucinogens and substances of abuse such as psilocybin, mescaline, lysergic acid diethylamide (LSD), and ketamine (Roth et al., 2002; Siebert, 1994; Valdes & Seymour, 1998). In contrast with these psychedelic substances, salvinorin-A does not interact with the serotonin-2A receptor (5HT<sub>2</sub>), but presumably induces its psychotropic effects through the activation of the  $\kappa$ -opioid receptors. Thus, *Salvia divinorum* is considered to be in a class of hallucinogen of its own (Gonzalez et al., 2006; Roth et al., 2002).

Although salvinorin-A is the main active principle in *Salvia divinorum*, other ingredients of salvinorin have also been identified. Salvinorin B-F has been identified in research, and although the function of these other ingredients is not well understood, they are thought to be rather benign or inactive. However, it has been suggested that salvinorin B may be a metabolite of salvinorin-A (Schmidt et al., 2005).

Because salvinorin-A is not water-soluble, it is mainly absorbed through the respiratory system and, to a lesser extent, by the oral mucosa (Bucheler, Gleiter, Schwoerer, & Gaerner, 2005). PET scan studies of baboons indicate salvinorin-A rapidly crosses the blood brain barrier (BBB), reaches 3.3% of the injected dose within 40 seconds, and will clear to half of peak by eight minutes (Hooker et al., 2008). Thus, the study reveals the extraordinarily rapid uptake and short duration of salvinorin-A activity in the body.

According to a study by Mowry, Mosher, and Briner (2003), salvinorin-A displays minimal physiologic effects. It was observed that body temperature, sympathetic nervous system activity, and cardiac effects are minimal with *Salvia divinorum* use. Moreover, there were no reports of cardiovascular events nor were there any symptoms that would suggest autonomic nervous system effects. Mowry et al. also investigated the toxicity of *Salvia divinorum* and the effects of repeated injections of salvinorin-A over time. The researchers injected mice with dosages well in excess of human consumption and found no histological changes. Thus, Mowry et al. found that long-term administration in mice seemed to confirm that salvinorin-A is a fairly benign substance with low toxicity. These findings should be interpreted cautiously, however, given that the study was limited in time and conducted on non-human subjects that demonstrate minimal psychological activity.

### ***Current Status***

The popularity of *Salvia divinorum* appears to have risen over the last ten years through its availability on the internet and its notoriety based on news reports. The internet, along with “smoke shops” or “head shops,” market *Salvia divinorum* as a legal alternative to marijuana, which appeals to marijuana users as well as adolescents who can legally buy the product under the age of 18 in many states and countries. Although the effects are dissimilar to that of marijuana, *Salvia divinorum* attracts a new following of individuals who want to experiment with a “safe” hallucinogen without engaging in illegal activity (Vince, 2006) or without experiencing longer-lasting psychoactive effects associated with other hallucinogens. However, a study by Wolowich, Perkins, and Cienki (2006) tested five samples of *Salvia divinorum* purchased from various retailers to test the purity of the substance. The researchers found variability within the samples and inconsistency in the labeling of the product prevented a

reliable determination of the amount of salvinorin-A concentration and extract consumed.

Samples tested included other substances not advertized, which suggests one cannot be sure that the product purchased is safe.

Salvia divinorum is currently legal in most states, but is banned in Delaware, Florida, Illinois, Louisiana, Maine, Missouri, North Dakota, Oklahoma, Kansas, Tennessee, and Virginia. Many states currently have legislation pending on restricting or banning Salvia divinorum. Most states that banned Salvia divinorum have done so only in the last few years. Salvia divinorum is also illegal in Australia, Finland, Denmark, Spain, and Norway, Belgium, Estonia, Italy, and Sweden (McDonough, et al., 2008; Singh, 2007).

### ***Prevalence***

According to a face-to-face interview survey by The National Survey on Drug Use and Health (NSDUH) about 1.8 million people age 12 or older have used Salvia divinorum in their lifetime, and approximately 750,000 did so in the year 2006. In addition, young adults ages 18 to 25 were nearly three times more likely than youths aged 12 to 17 to have used Salvia divinorum. The study also found that males were 3 to 4 times more likely to have used Salvia divinorum than females (Substance Abuse & Mental Health Services Administration Office of Applied Studies, 2008).

The first study of Salvia divinorum use in college students was conducted by Lange, Reed, Ketchie-Croff, and Clapp (2008), with data obtained in 2006 through 2007. They concluded that Salvia divinorum use in college students (4.4%) was comparable to that of other illicit drugs such as ecstasy (5%) and cocaine (7.1%). However, there are a number of shortcomings in the study. First, it consisted of students from a single university that completed internet based self-report measures. Moreover, the results could have been further hindered based

on the state legal restrictions on *Salvia divinorum* and could show differing rates due to the legality and availability of the substance (Lange et al., 2008)

In another study of college students, Khey, Miller, and Griffin (2008) found that an overwhelming majority 81.9% reported learning about the drug through their friends, and 4.8% learned about the substance from a class, while only 2.7% of student learned about *Salvia divinorum* via the Internet. Thus, *Salvia divinorum* is not primarily an internet phenomenon, as previously thought. Indeed, internet sales accounted for only 9.1% of the total *Salvia divinorum* sales, and that the vast majority (77%) of *Salvia divinorum* was purchased from stores or “head shops.” In addition, the study suggests that *Salvia divinorum* use occurs more often in groups than used on an individual basis, lending it to be more of a social activity. Khey et al. concluded that although *Salvia divinorum* use does exist within a college population, use occurs most often in white male students from wealthy backgrounds, along with those who use marijuana on a regular basis. Based on the findings of this survey, it may be hypothesized that the media attention given to *Salvia divinorum* may increase interest in the substance along with possibly increasing its use and prevalence (Khey et al., 2008). However, the study consists of several limitations which may have an impact on the findings. First, the study was conducted at a single university which may consist of a particular demographic such as, culture, SES, gender, or race. Secondly, in terms of purchasing the substance from a store versus the internet, it is possible the results were swayed based on availability. For example, it is possible a “head shop” was within walking distance of the university which suggests students are more likely to have purchased the product from a store. Another limitation in the study is the use of self-report measures in a college setting. It is possible the sample was gathered using collusion or secondary gain, such as extra credit provided for participating in the study versus participating voluntarily.

### *Subjective Experience*

Siebert (1994) concluded the effects experienced by Salvia divinorum users depends on factors such as dosage and setting. He found that people frequently report seeing visions of people, objects, or places; and with dosages exceeding 1mg may experience out of body sensations. While in the midst of the psychoactive effects, he reported that people will get up and move around with no apparent awareness of their movements or behavior, may speak gibberish, or laugh hysterically. Siebert goes on to list several common themes with examples of visions or sensations experienced by Salvia divinorum users which include: (a) becoming objects, (b) visions of two dimensional surfaces, films, or membranes; (c) revisiting places in the past such as childhood; (d) loss of body or identity; (e) sensations of motion; (f) uncontrollable laughter; or (g) overlapping realities.

Gonzalez and colleagues (2006) obtained systematic information on the pattern of use and the nature of the subjective effects elicited by Salvia divinorum in recreational users. Self-report questionnaires that included the Hallucinogen Rating Scale (HRS), the State Trait Anxiety Inventory-S (STAI-S), and the Altered States of Consciousness Questionnaire were administered to 18 male and 14 female participants with a mean age of 25 to obtain demographical and subjective effect information of Salvia divinorum use. Results of the study found that 88% first used the substance within the last year, with an average use of two times. Moreover, all participants reported having smoked the substance in extract-form over chewing the leaves.

Regarding their experience while using the drug, 75% described the experience as “intense” “very intense” or “extremely intense.” The reported positive effects included the “trip” (41%), euphoria (28%), and the dissociation (19%) elicited by the substance. Negative effects endorsed by participants included the short duration of effects (38%) and lack of control over the

experience (16%). Forty-four percent of participants reported some degree of malaise, hang-over, mental fatigue, or comedown immediately after the acute effects of use. Forty-four percent of participants reported that they would like to use *Salvia divinorum* regularly. Most participants (63%) reported that the effects of *Salvia divinorum* were most similar to those of psilocybin mushrooms (55%). Of note, only 20% of participants reported the effects to be similar to that of marijuana, which is interesting given that *Salvia divinorum* has been traditionally marketed as an alternative to marijuana (Gonzalez et al., 2006).

The study had several substantial limitations. First, the sample size was small. Second, self-report subjects may exhibit a tendency to over- or under-report substance use. Third, many participants reported regularly using other drugs, and thus some of the effects may have been due to other substances. Lastly, researchers were unable to control dosage of the drug.

In a web-based study of 500 users, it was found that after-effects of using *Salvia divinorum* included feelings of increased insight (47%), improved mood (44.8%), calmness (42.2%), and an increased sense of connection with the universe or nature (39.8%). In addition, 25.8% of participants reported persisting positive effects felt 24 hours after use which usually include an increased sense of well-being (Baggott, Erowid, Erowid, & Mendelson, 2004).

### ***Purpose of the Present Review***

Although *Salvia divinorum* has been used for a number of years in the Mazatec culture for medicinal and spiritual purposes, use in the United States for recreation has been fairly recent. Despite advancements in salvinorin-A research, little is known about *Salvia divinorum* and its effects on the body. The vast majority of research on *Salvia divinorum* appears to be related to the plant's pharmacology and chemical composition, while few studies have examined the short-term and long-term effects or potential impact on psychological functioning. Some

researchers suspect that the drug may provide a number of benefits in the future, based on the active component and its action on  $\kappa$ -opioid receptors. For example, researchers have suggested that the study of *Salvia divinorum* may advance knowledge and treatment of schizophrenia, depression, bipolar disorder, and certain types of dementias like Alzheimer's, Huntington's, and Pick's diseases may be derived from research with salvinorin-A. Furthermore, drug abuse of certain substances such as cocaine may be better understood and medically treated with medication designed to work on the  $\kappa$ -opioid receptors in the brain. Moreover, activation of the  $\kappa$ -opioid receptors induces a number of behavioral effects such as analgesia and sedation (Roth et al., 2002), which suggests its potential use as a pain reducer.

Despite the potential benefits of studying *Salvia divinorum*, many questions related to the substance remain unanswered. Unfortunately, there are political, legislative, and social decisions to consider based on the limited or lack of research on *Salvia divinorum*. In addition, public image of *Salvia divinorum* tends to be negative in large part due to internet posted videos on YouTube which portray the herb in a disturbing manner. Adolescents and young adults post public videos that show irresponsible and immature behavior. These videos show users in a trance-like state or appearing to have seizure-like symptoms and often end with the users experiencing a "bad trip." These legislative decisions and laws restricting or banning *Salvia divinorum* often limit or eliminate the ability to research and study the active principle in *Salvia divinorum*, thus losing potential benefits the substance may offer to medicine. Therefore, the purpose of the current review is to critically evaluate the literature and research available related to the potential effects *Salvia divinorum* has on cognitive, affective, and behavioral functioning in humans. Based on this review, the author will provide recommendations in areas for improvement and future research. Furthermore, the review will act as a comprehensive review of

the history, background, and research of *Salvia divinorum* for use in future studies and for the purpose of educating clinicians and the general public about *Salvia divinorum*.

## Chapter 2

### Review of Empirical Literature on Salvia Divinorum

#### *Cognitive Functioning: Introduction to the Cognitive Process*

The author will begin the present review by focusing on research pertaining to how Salvia divinorum impacts cognitive functioning. For the purpose of this critical literature review, cognitive functioning will be defined as the process and activity which takes place in the regions of the brain during Salvia divinorum use. It will include areas in the brain where studies have shown that salvinorin-A is active during use. The author will review research that identifies cognitive activity associated with Salvia divinorum use, along with studies related to human perception and how it may impact an individual's emotions and behavior. As such, cognitive functioning is considered interrelated with affective and behavioral processes. For example, the discussion may focus on how hallucinations impact an individual's thought process, but may also impact behaviors and emotional state as well.

***Cognitive/subjective effects of Salvia divinorum.*** A prominent feature of Salvia divinorum use is the psychoactive and hallucinogenic effects. Cognitive and subjective effects that have been reported in studies include but are not limited to feelings of euphoria, dissociation, increased insight, unusual thoughts, depersonalization, disconnection from reality, hallucinations or colored visions, and loss of consciousness (Baggott et al., 2004; Bucheler et al., 2005; Gonzalez et al., 2006; Siebert, 1994).

In a case study, Bucheler et al. (2005) interviewed a 19-year-old high school student who reportedly had been chewing and smoking Salvia divinorum approximately twice a week for approximately six months. The student reported depersonalization and widening of consciousness, as well as difficulty learning or memorizing school assignments. The individual did not attribute the memory difficulties to the drug itself, rather considered it a result of needing

to reflect on his perceptual experience. The single case study not only demonstrates the psychoactive effects of *Salvia divinorum*, but also the impact on cognitive functioning after using the substance.

***Salvinorin-A and activation of  $\kappa$ -opioid receptors in cognition.*** As previously mentioned, salvinorin-A is a potent and highly selective  $\kappa$ -opioid agonist that has little resemblance to classical hallucinogens (Roth et al, 2002). Human studies with selective  $\kappa$ -opioid agonists have shown that activation of the receptors induce visual distortions and depersonalization (Walsh, Strain, Abreu, & Bigelow, 2001). Therefore, the  $\kappa$ -opioid receptor system plays a prominent role in the modulation and regulation of human perception and cognition (Roth et al., 2002). Taken together, this suggests that *Salvia divinorum*, or more specifically salvinorin-A, has a profound effect on perception and logical thinking.

***Salvinorin-A,  $\kappa$ -opioid receptors, and brain locations.*** Hooker et al. (2008) used Positron Emission Tomography (PET) to measure the pharmacokinetics and distribution of salvinorin-A within the brain and peripheral organs of six female baboons. They found that salvinorin-A quickly entered the brain and attained maximum concentration within 40 seconds. In addition, it was observed to clear the brain rapidly with a half-life peak of 8 minutes. Furthermore, salvinorin-A was widely distributed throughout the brain in both the cortical and subcortical regions. They found the highest concentration of salvinorin-A in the cerebellum and visual cortex, which may account for *Salvia divinorum*'s hallucinogenic effects. Hooker et al. (2008) estimated that less than 10 mg of salvinorin-A in the human brain could account for the psychoactive properties of *Salvia divinorum*.

Hooker, Patel, Kothari, and Schiffer (2009) investigated downstream effects of salvinorin-A such as changes secondary to neuron activation. The goal of their study was to

identify brain regions and neural circuits associated with salvinorin-A mediated effects. They used a PET scan to examine regional changes in 19 rat brains. Using this technique, their research provided the first map of cerebral metabolic activation along with behaviors in rodents. Their findings demonstrated increased metabolic activity in the periaqueductal gray, bed nucleus of the stria terminalis, and cerebellar vermis. Furthermore, neural activity was not limited to regions associated with a high density of  $\kappa$ -opioid receptors. Significant bilateral activations were also observed in areas of the brain which had little to no  $\kappa$ -opioid receptors, such as the hypothalamus and auditory, sensory, and frontal cortices. Moreover, increased activity was also seen in the left ventral pallidum which is located within the basal ganglia, and right lateral geniculate nucleus which is part of the thalamus. Furthermore, decreases in metabolic activity were observed in the caudate putamen, superior colliculus, hippocampus, and medial brainstem. These findings by Hooker et al. indicate that the response to salvinorin-A in the brain goes well beyond the immediate  $\kappa$ -opioid receptor effects, and involves a larger and more complex network of neural connections and activity which respond to the initial  $\kappa$ -opioid receptor effects. For instance, activation of the  $\kappa$ -opioid receptors can cause an increase or decrease in metabolism that result in additional activation or inhibition of neural systems in various regions of the brain.

Zhang, Butelman, Schlussman, Ho, and Kreek (2005) observed the effects of salvinorin-A on dopamine levels in the caudate putamen and nucleus accumbens. They also attempted to find a salvinorin-A induced conditioned place aversion, along with studying changes in locomotor behaviors in mice. They found that higher doses of salvinorin-A (1.0 mg/kg and 3.2 mg/kg) significantly decreased dopamine levels in the caudate putamen, but not in the nucleus

accumbens. They concluded the inhibitory effects of salvinorin-A on dopamine levels may contribute to a conditioned place aversion and a decrease in locomotor activity in mice.

In contrast, Braida et al. (2009) studied the effects of salvinorin-A in rodent models of emotional behavior. They found evidence of anxiolytic and antidepressant effects of salvinorin-A in rats. Furthermore, their experiments rendered a salvinorin-A-induced increase in dopamine levels in the nucleus accumbens, which they suggest may be involved in the modulation of affect and motivation.

Chartoff, Potter, Damez-Werno, Cohen, and Carlezon (2008) investigated the mechanisms of  $\kappa$ -opioid receptor modulation of striatal function and the potential co-morbidity to cocaine addiction. One of their findings suggests salvinorin-A was active in the nucleus accumbens, prefrontal cortex, hippocampus, and central and lateral amygdala. They theorized that activity in these limbic brain regions may mediate the cognitive effects of salvinorin-A.

Research by Peckys and Landwehrmeyer (1999) states that  $\kappa$ -opioid receptors located in specific areas of the brain could mediate sedative-like effects. These target areas for sedative effects of *Salvia divinorum* include the prefrontal cortex, dorsal and ventral striatal area, lateral hypothalamus.

### ***Affective Functioning: Introduction to the Affective Process***

As previously mentioned, the three areas of exploration (i.e., cognition, affect, and behavior) are not separate entities. Indeed, cognitive process influences perception and thereby affective experience. For the purpose of the literature review, the definition of affective functioning is the process of emotions and feelings that occurs during and after the use of *Salvia divinorum*.

***Reported affective responses to Salvia divinorum.*** Common affective responses to Salvia divinorum have been associated with positive feelings and include euphoria, laughter, calmness, and improved mood (Baggott et al., 2004; Bucheler et al., 2005; Gonzalez et al., 2006 Siebert, 1994). In the Bucheler et al. (2005) case study, a male teenager reported experiencing an extracorporeal existence in a new “astral body,” which he reported provides a “good” feeling of recreation. However, not everyone who has used Salvia divinorum reported positive feelings. Perceptual distortions can lead to feelings of fear and insecurity. People may experience horror, panic attacks, and anxiety (i.e., “bad trips”). These are believed to be largely due to the loss of self-control, inability to interact with environment, and disconnection from reality (Bucheler et al., 2005; Gonzalez et al., 2006). However, in a study by Braida et al. (2009) low doses of salvinorin-A were found to have a slight anxiolytic effect in rodents. Thus, lower doses of salvinorin-A may produce an anxiolytic effect while higher doses which produce hallucinations that may increase anxiety in relation to the psychoactive effects. In addition, dosage and setting contribute to the type of experience the user encounters, and it is believed that Salvia divinorum may have only a weak influence on the prevailing mood of the user (Siebert, 1994).

***Salvinorin-A and depression.*** It has been suggested that substances that affect the  $\kappa$ -opioid receptors can cause alterations in the mood of humans (Pfeiffer, Brantl, Herz, & Emrich, 1986; Roth et al. 2002). Due to the effects of salvinorin-A on human cognition and the influence of the substance in the limbic areas of the brain, it is believed Salvia divinorum may have a role in modulation of emotions. Many researchers believe Salvia divinorum may be helpful in treating mood disorders due to the ability of salvinorin-A to target specific receptors in the brain, such as  $\kappa$ -opioid receptors and not the  $\mu$ - or  $\delta$ -opioid receptors or serotonin-2A receptor (5HT<sub>2</sub>).