Chapter 3
Ayahuasca as a Candidate Therapy for PTSD

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Abstract Posttraumatic stress disorder (PTSD) is a syndrome that affects a substantial portion of both the civilian and military populations, and is often underdiagnosed due to complications with delayed onset and co-occurring psychiatric disorders. The prevalence of this devastating disorder is growing as more people come forward with traumatic events in their past. It is crucial that we develop a more comprehensive diagnostic and therapeutic framework for PTSD in order to reduce harm and aid in long-term functional recovery. Currently accepted therapeutic options for PTSD are proving to be insufficient as increasing numbers of people present with treatment-resistant PTSD, and alternative avenues for diagnosis and treatment are currently being investigated to improve standards of patient care. This chapter focuses on the rationale for why ayahuasca may be successful in treating certain kinds of PTSD, and reviews the previously reported pathophysiology of PTSD and its current treatments, and the new, experimental therapies being explored. This chapter also proposes a novel method known as "syndromics," which aims to characterize the full syndrome of PTSD using bioinformatics and multivariate pattern detection, in the hopes that by understanding the full complexity of this syndrome, we will be able to identify more efficient therapeutic targets, such as ayahuasca, to cure it.

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Relevance

> It is to our detriment that we live in a culture that does not honor the internal world. In many cultures, the internal world of dreams, feelings, images, and sensations is sacred. Yet, most of us are only peripherally aware of its existence. We have little or no experience of finding our way around in this internal landscape. Consequently, when our experience demands it, we are unprepared (Levine and Frederick 1997).

Posttraumatic stress disorder (PTSD) is a debilitating syndrome that causes extreme states of fear as the result of a deeply distressing experience (American Psychological Association 1994; Yehuda 2002). It is estimated that approximately 40−60 % of adults have been exposed to a traumatic experience, and approximately 7−12 % of them will develop PTSD (Stein et al. 2000). However, among combat veterans, this statistic increases to 22−31 % (Prigerson et al. 2002), and may be an under-representation of the actual prevalence of PTSD, as symptoms often go unrecognized for years as clinicians and patients struggle to conceptualize the intrinsic experience of the patient. Diagnosis is further complicated because PTSD symptoms often remain undetected under co-morbid conditions such as substance abuse, major depressive disorder, somatization disorder, and other anxiety spectrum disorders (Johnson 2009). PTSD is underdiagnosed in both medical and psychiatric clinical practice (Zimmerman and Mattia 1999). This is confounded by the harsh reality of the rapidly increasing suicide rate among members of the military (Dao and Lehren 2013). This is a wake-up call to us all to develop a better framework for diagnosing and treating these patients to maximize long-term recovery and quality of life, and reduce the risk of abuse, relapse, and suicide.

Within both the military and civilian populations, the stigma of PTSD is a serious issue preventing help-seeking and reducing quality of life (Gould et al. 2007). Often the most stigmatized and difficult to treat mental illnesses are also the ones best managed by controlled substances. When prescribing controlled substances, clinicians are faced with an ethical battle. Because of the potential for misuse of these medications, leading to substance abuse, clinicians often under-treat patients well managed by controlled substances (Longo and Johnson 2000; Longo et al. 2000). This results in misdiagnosis and neglectful treatment of those with complicated mental health disorders like PTSD. Additionally, federal regulation of controlled substances makes using them for research purposes difficult (Dolan 2011), and slows progress toward exploring the therapeutic potential that some of these substances may have for complicated disorders of the mind and body. Although this does not suggest that every substance should be used in medicine, it does suggest that exploration of these substances may hold the key to unleashing what current medicine has failed to provide a solution.

There are a number of controlled substances being tested by a growing number of researchers for the treatment of PTSD, including 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy (Mithoefer et al. 2011, 2013; Oehen et al. 2013) and agonists of the endocannabinoid system (Neumeister et al. 2013).

However, this chapter focuses on the potential of ayahuasca as a candidate for treatment of PTSD. Ayahuasca is an Amazonian tea that contains dimethyltryptamine (DMT), among other constituents. Ironically, DMT is a controlled substance in the Western world, and its potential production in the human body has been thoroughly reviewed (Barker et al. 2012), though its source and function are still poorly understood.

We hypothesize that the mechanism of ayahuasca's therapeutic benefits mimic currently available psychotherapies. Different than therapy that requires communication with a clinician, an added value of the ayahuasca journey is that it takes individuals into a realm where they can be without pressure to explain what is beyond their intellectual capacity. In this realm, victims can be fully present to experience all emotional and sensational elements of their traumatic patterns, allowing them to finally find resolution with their past without the distraction of having to articulate details they struggle to comprehend on a conscious level. Here, we review the pathophysiology that has previously been reported about PTSD and the rationale for the potential therapeutic benefits ayahuasca may provide for PTSD, based on the psychopharmacologic and psychotherapeutic aspects of ayahuasca.

What is PTSD?

A review of the involvement in memory formation and the development of PTSD and the pathology of trauma is required to understand the pharmacologic and therapeutic potential of ayahuasca for PTSD.

The memory system. Human memory, formed by the limbic system, can most simply be divided into implicit and explicit memories. Once the memories are formed, they are stored in the prefrontal cortex for future retrieval. Implicit memories are processed by the amygdala. These are somatic memories that do not require conscious awareness, such as remembering how to ride a bike or tie one's shoelaces. Explicit memory is our conscious memory; it is where we make cognitive sense of our memories and are able to recall previous experiences and information. The hippocampus is where explicit memories are processed so that they can later be retrieved from storage in the prefrontal cortex (Stickgold 2002). Traumatic experiences create an implicit memory without an explicit memory to consciously make sense of it. The body remembers what the conscious mind cannot. Therefore, when a victim experiences stimuli reminiscent of the traumatic event, she or he has sensations similar to those associated with the original experience. This can be re-traumatizing for the subject when overwhelming fear and anxiety return as if they were in the initial moment of victimization all over again. However, this type of response can also lead to catharsis in the form of extinction, which is the purpose of exposure therapies. By experiencing the memory of the trauma in a safe and therapeutic environment, subjects can tune themselves to respond differently to the triggers and move past their debilitating side effects

(Ursano et al. 2004). The primary goal of treatment for PTSD is to free subconscious memories to be meaningfully processed and integrated into the victim's life without replicating the disorienting emotional intensity.

The development of PTSD. The hypothalamus-pituitary-adrenal (HPA) axis is the body's stress response system. Its primary functions, in relation to trauma, are to guide emotions that stimulate instinctual behavior for survival (the "fight or flight" response), and to process memories. Stressful stimuli are first sensed by a part of the limbic system called the amygdala, which goes on to activate the HPA axis. In a normal response to stress, there is a negative feedback mechanism to turn the HPA axis off when there is no longer a threat. Trauma, however, disrupts the negative feedback mechanisms of the HPA axis, so that the body is in a chronic state of arousal. This chronic arousal state suppresses the hippocampus, preventing the formation of explicit memory, thus trapping traumatic memories in the implicit system. This is what underlies PTSD. The images, emotions, and somatic sensations can all be provoked, but without explicit memory, they cannot be articulated or understood. The persistent arousal of the stress response system leaves the body and brain unable to differentiate past from present (Johnson 2009).

Symptoms of PTSD are a manifestation of a victim's attempt to interpret internal states that are often difficult for the patient to describe, and even more difficult for the clinician to interpret and treat, resulting in a barrier against translating the internal state of these patients for those trying to treat them. PTSD poses another challenge to psychiatry, with its high rates of treatment resistance, both in the form of ineffective therapies and due to subjects' hesitation to accept treatment for a highly stigmatized disorder (Gould et al. 2007). This resistance to treatment often leads trauma survivors to develop their own maladaptive coping mechanisms, such as substance abuse and antisocial behaviors, to suppress debilitating symptoms. In turn, these coping mechanisms often lead to an exacerbation of their symptoms, creating a negative feedback loop that can be like a runaway train of fear and anxiety, leading those who suffer from PTSD toward extreme ends, including suicide. This is known as "maladaptive plasticity," and functions as a strong opposition to the positive feedback loop needed to promote functional recovery.

Maladaptive patterns of PTSD cease when subjects slow down and experience all of the elements of sensation and the feelings that accompany them. If victims allow themselves to acknowledge the thoughts and sensations associated with their traumas, the perceptions will have their natural flow, peak, and then begin to diminish and resolve, allowing the nervous system to regain its capacity for self-regulation (Levine and Frederick 1997). Maladaptive plasticity has been extensively modeled at the preclinical level in trauma paradigms, both in learned helplessness (LH) animal models of PTSD (Grau et al. 1981; Petty et al. 1992; van der Kolk et al. 1985) and following attempts to understand spinal learning following spinal cord injury (SCI) (Ferguson et al. 2012a, b; Grau et al. 2012). Maladaptive spinal learning following SCI shows the same physiological responses as the maladaptive coping mechanisms seen after a psychological trauma, leading to the development of PTSD. Adaptive plasticity occurs as the nervous system attempts to adapt after a severe trauma has occurred. The goal is to learn from the

limitations, re-tune the neural connections, and identify behavioral modifications that will strengthen and reinforce these connections to maximize recovery and reduce additional harm. Due to the fact that the serotonergic system is affected by trauma, we believe that targeting this system therapeutically may be the key for modulating the downstream effects of trauma, as reviewed below. We hypothesize that this puts the nervous system into a "tuning" state where physiological patterns can be modified. The process of modulating the nervous system is known as "plasticity" and has been extensively studied within the contexts of learning and memory (Shepherd and Bear 2011), and response to trauma (Wang and Sun 2011). In understanding how the nervous system adapts, we can unlock the mechanisms that are necessary to steer those adaptations toward the direction of healing, recovery, and growth.

This tuning occurs both after trauma, when maladaptive plasticity takes control after serotonergic activity is reduced, and following treatment with serotonergic agonists, which may promote "metaplasticity" (the plasticity of plasticity). This is what we are referring to as `tuning': The ability to change the way the system changes in response to a stimulus. If this is done during a time of plasticity (i.e., tuning), there is an opportunity to modify the connections of the system (e.g., learn a new task), and establish a new pattern of activation that will reinforce the new behavior (integration). For PTSD, the addictive and antisocial behaviors can be seen as the maladaptive component of this plasticity. If gone improperly treated and unchecked, it can spin out of control and away from healing. However, this tuning period can also be directed toward positive reinforcement. In the tuning phase, the subject has the opportunity to choose a path to integrate what is being set forth during this stage. They can choose to walk down the path of coping mechanisms, including drug addiction and antisocial behaviors, solidifying their debilitating symptoms. Or they can choose the more difficult, yet more rewarding path of establishing new patterns reinforced with integrative exercises, such as psychotherapy, to implement the changes in their life needed to move through the downstream effects of their trauma.

This translation of maladaptive plasticity in both SCI and PTSD taps into the core nature of trauma itself, whether physical or psychological, and involves the serotonergic system as a key modulator of this plasticity.

Serotonin and PTSD. Following PTSD (Murrough et al. 2011) and SCI (Hains 2002), there is decreased serotonergic activity that reduces the effects of naturally occurring serotonin (5HT) signaling. Decreased serotonin affects the body's ability to modulate arousal, resulting in an exaggerated startle response to stimuli. In addition, it leads to further dysfunction in regulation of the amygdala, hippocampus, and prefrontal cortex. The goal of most therapies targeting this effect is to flood the system with serotonin using selective serotonin reuptake inhibitors (SSRIs), boosting the function of this system, which is involved in the activation of stress (Jones and Moller 2011) and modulation of pain (Hains et al. 2002), both of which greatly contribute to the debilitating consequences of physical and psychological trauma. Drugs that target the serotonergic system are already being tested to treat depression, PTSD (Murphy 2010), and pain (Dharmshaktu 2012). Serotonergic

agonists like MDMA, DMT-containing ayahuasca, and 2,5-dimethoxy-4-iodoamphetamine (DOI) have shown promising results to treat a wide range of complications from trauma, including PTSD (Bouso et al. 2008; Mithoefer et al. 2011, 2013; Oehen et al. 2013), drug addiction (Thomas et al. 2013), and spinal cord injury (Lyalka et al. 2011), respectively. Therefore, psychedelic substances like DMT-containing ayahuasca should be explored as candidates to test serotonergic-mediated adaptive plasticity on recovery from trauma.

Treatment of PTSD

Current treatments for PTSD. Antidepressants are the first line psychopharmacologic treatment for PTSD (Johnson 2009). Specifically, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) manage symptoms that result from alteration in serotonin pathways. Modulation of the serotonergic system has been shown to be effective in both psychological and physical models of trauma. Somatic-based therapies also play a prominent role in healing trauma. A blockage of undischarged arousal in the body's somatic nervous system is a result of the memory disruption in PTSD. Symptoms of anxiety arise to contain and discharge the blocked arousal. However, anxiety does not resolve the underlying somatic freeze. In order to achieve resolution of traumatic events, arousal symptoms must be discharged on the somatic sensory level where the information was first stored (Johnson 2009). Levine suggests that the first step toward resolving trauma is to work with unresolved impacts through the felt sense (Levine and Frederick 1997). The felt sense is perceived by bringing awareness inside the body to the sensory and emotional landscape. It moves focus to the present internal experience. The awareness of the felt sense provides victims with a gentle energetic discharge just as effective as that which is accessed through action in non-pathological reactions to threat (Levine and Frederick 1997).

Exposure therapy is the fastest acting psychotherapy, and one of the most effective, targeting traumatic memories of PTSD (Johnson 2009). During exposure therapy, patients are exposed to a feared object, or context, without the danger. The exposure allows them to re-experience the traumatic event in a safe and controlled environment, creating an opportunity to integrate information and resolve the pathological memory. The intensity of distress associated with disturbing implicit memories is decreased through the confrontation of situations, people, and emotions associated with traumatic triggers. The confrontation allows victims to identify, reorganize, and neutralize environmental cues (Johnson 2009). Eye Movement Desensitization and Reprocessing (EMDR) is a Food and Drug Administration approved evidence-based therapy for PTSD with an exposure component (Ursano et al. 2004). In EMDR, the patient is asked to focus on eye movements, hand taps, and sounds while the disturbing images, negative cognitions, and bodily sensation

associated with the traumatic memory are brought to mind. EMDR helps change the reaction to memories by reducing the disturbing thoughts that have not been discharged or released.

We believe that current therapeutic options for those who suffer from PTSD are insufficient, due to the high incidence of treatment resistance and suicide already discussed, suggesting that new treatment options need to be explored. Conventional medicine has shifted its focus to rely on the intellect as the agency of care (Lewis et al. 2000). Because humans are most aware of their intellect, it is falsely assumed that the problem lies within the intellect, and this is where it can be solved (Levine and Frederick 1997). Emotions are rarely considered in pathophysiology; however, the very core of the traumatic reaction is emotional. Progress cannot be made with the PTSD patient until he or she is able to discuss the traumatic event without replaying the memory accompanied by its sensory and affective intensity.

Embarking on the journey to transformation requires courage, as it is not possible to escape reliving the emotional experiences victims most wish to rid themselves of. Due to the emotional volatility that accompanies resolving trauma symptoms, PTSD interventions must prioritize a safe and secure environment. The type of integrative therapy that is used must also be determined prior to treatment, since certain triggers may prevent recovery. Although it may seem intuitive for people who have been paralyzed by SCI to maintain an active stretching routine in physical therapy to reduce muscle pathology, this method has not proven to be beneficial, and animal models suggest it may even prevent recovery (Caudle et al. 2011), perhaps due to activation of maladaptive patterns that cause more harm than good. This suggests that the kind of therapy that triggers this kind of stimulation in PTSD (i.e., re-experiencing, exposure therapy) may prevent victims from recovering. This reaction is so strong that it could explain why some people are treatment resistant.

Ayahuasca for PTSD Treatment

Experimental therapies currently under investigation for PTSD include MDMA-assisted psychotherapy (Bouso et al. 2008; Mithoefer et al. 2011, 2013; Oehen et al. 2013), modulation of the endocannabinoid system (Neumeister et al. 2013), and anecdotal (Fig. 3.1a) and complementary (Thomas et al. 2013) evidence for ayahuasca for PTSD. The treatment of addiction with ayahuasca is considered complementary to treatment of PTSD in consideration of the fact that many PTSD patients have substance abuse disorders (SUDs) (Saladin et al. 1995). Brain imaging studies in humans suggest that ayahuasca significantly activates frontal and paralimbic brain regions, specifically the left amygdala and parahippocampal gyrus (Riba et al. 2006). These regions play a prominent role in emotional processing and memory formation. As reviewed earlier, the amygdala processes implicit memories and the hippocampus explicit memories. Ayahuasca's activation of the hippocampus can allow for implicit memory formation previously disrupted by a traumatic event. During an ayahuasca journey, victims have the opportunity to

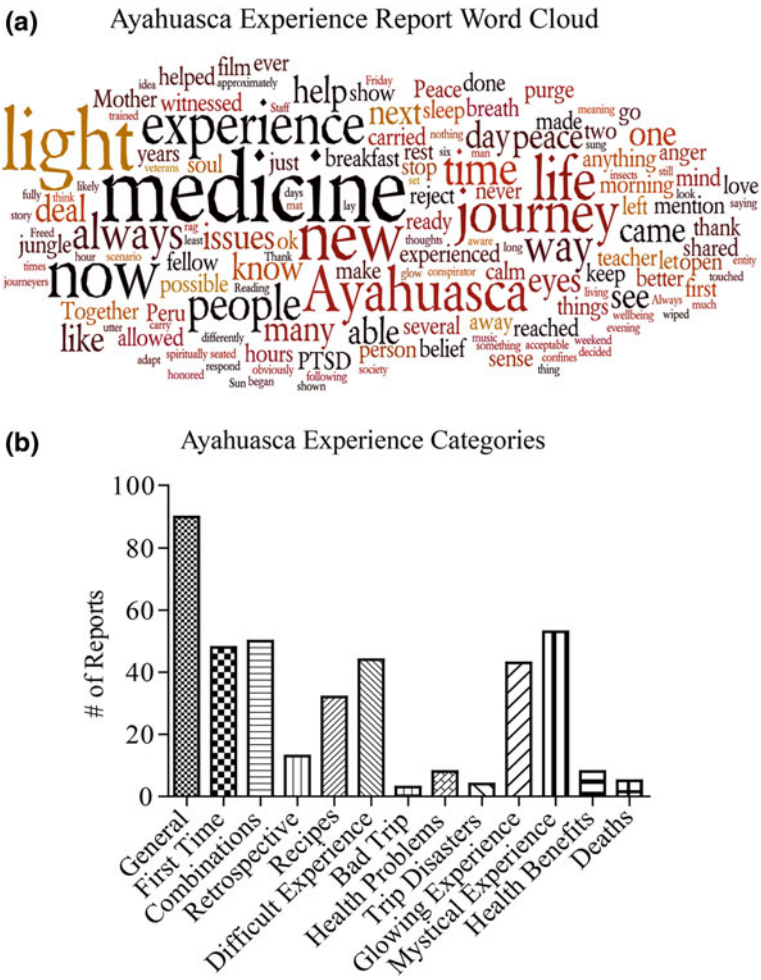


Fig. 3.1 Quantification of ayahuasca experience reports. Word frequency clouds (**a**) generated from Wordle™ from reports posted on Facebook by war veterans using ayahuasca to treat their PTSD (n = 3). Subjects taking ayahuasca for PTSD generally had a positive description of their experience and specifically referred to ayahuasca as "medicine." To get a better sense of anecdotal experiences of ayahuasca, regardless of the intentions of the experience, additional ayahuasca experience reports were mined from Erowid (2012) and plotted as a number of reports per experience category (**b**). Classification of experiences showed a trend towards positive experiences (e.g., glowing, mystical), with a comparable number of difficult experiences. However, there were far less "bad trips" reported, as opposed to difficult experiences, and the number of deaths affiliated with ayahuasca use were also minimal (Erowid 2013)

change how they react to memories in ways similar to exposure therapy and EMDR. The following is an account of a trauma victim's ayahuasca experience, reproduced with permission:

> A major aspect of working with aya [ayahuasca], is reliving trauma. The beauty of the experience of the medicine is that while the environment is contained and quite safe, especially while under the guidance of a healer, it is still psychologically compelling and transformative. For example, the idea that you are about to die or are dying is quite common while using aya. The individual has a choice to accept and make peace with this. Now, despite the fact the individual was not actually dying, the psychological result is the same: He faced death and made peace with it and can now incorporate this into life. I had a very powerful experience where I was forced to relive a traumatic memory repeatedly until I no longer held any negative energy toward it. It resulted in my ability to view the memory without the negative reaction I previously held (2013, Personal Communication).

Although it may seem counterintuitive to reactivate the HPA axis to aid in healing, as described in exposure therapies, if done in a safe, controlled environment, it creates the opportunity to identify, reorganize, and neutralize triggers and symptoms. Preliminary evidence from several war veterans with PTSD who participated in ayahuasca ceremonies at a healing center in Peru (n = 3) suggests that ritualized ayahuasca therapy can be a beneficial treatment for PTSD symptoms. Experience reports posted on Facebook by these subjects were mined and assessed in a word frequency cloud developed in Wordle™ (Feinberg 2013) to determine whether a healing theme could be derived from their experience of their treatment (Fig. 3.1a). This word cloud suggests that they viewed ayahuasca as a form of medicine to treat their PTSD, and the general theme trended toward positive experiences. Additional experience reports mined from Erowid and plotted as number of reports per category (Fig. 3.1b) reveal a comparable number of difficult experiences compared to both glowing and mystical experiences, as well as equal numbers of health problems and benefits, though these trended on the lower scale of total reports (Erowid 2012). Prior studies have shown ayahuasca to be safe under the appropriate conditions (McKenna 2004), however a handful of deaths have been associated with the use of ayahuasca (Fig. 3.1b) (Erowid 2013), and therefore appropriate measures, such as screening for contraindicated drugs and preparedness for this kind of therapy, should be utilized prior to consideration of this as a therapy.

Previous research indicates that ayahuasca administration causes robust activation of the HPA axis (Dos Santos et al. 2011), and thus may further aid in healing trauma. Studies have shown that ayahuasca is a serotonergic agonist (Riba et al. 2002), similar to SSRIs and SNRIs. Additional research has also found that regular ayahuasca use results in long-term modulation of serotonin systems in the brain (Callaway et al. 1994). Since the serotonin transporter is involved in multiple mental health disorders, it is hypothesized that there is a link between the elevation of serotonin transporters seen with long-term ayahuasca use and positive behavior changes.

Sensation is the language of the reptilian brain (Levine and Frederick 1997), and emotion the language of the mammalian brain. Through the activation of the limbic system and the HPA axis, ayahuasca communicates fluently with areas of the human brain that need nurturing to heal. During the ayahuasca journey, individuals can explore sensations, emotions, and thoughts associated with trauma, so that symptoms are discharged and resolved. Ayahuasca also guides victims to resolve events that predispose them to PTSD. “Complex trauma” is chronic interpersonal

trauma in childhood that occurs within the caregiving system, such as with sexual and domestic violence. It is a significant risk factor for the sequela of PTSD with exposure to future traumatic events (Blaustein et al. 2003). The impact of prior traumas on resilience indicates that psychotherapeutic interventions aimed at integrating and diminishing the effects of traumatic experience must target not only the precipitating trauma, but remote trauma as well (Ursano et al. 2004). Complex trauma is an important target for intervention, as proper neurodevelopment is achieved through synchronizing the nervous system with attachment figures. After birth, the mother and child communicate and exchange with each other via the regulation of each other's limbic minds (Lewis et al. 2000). Emotional learning happens implicitly. Without synchronization with primary attachment figures, children lose their capacity to adequately regulate physical and emotional states (Blaustein et al. 2003). Similar to the limbic regulation that may occur between mother and child, successful therapeutic interventions are achieved when patient and therapist interact on an emotional level to develop and strengthen pathways that were dysregulated or insufficiently developed. Psychotherapy changes people because one person can help restructure the limbic brain of another, leading to greater emotional health (Lewis et al. 2000). Ayahuasca opens the limbic pathways of the brain to affect the emotional core of the trauma in a way similar to affective psychotherapy for trauma, and also impacts higher cortical areas (de Araujo et al. 2012; Riba et al. 2006) to allow the patient to assign a new context to their trauma to help them understand and move through it. Physiologically, we see activation of the same emotional brain centers with ayahuasca administration as we do in attachment relationships. Ayahuasca has the capacity to go a step beyond the event that precipitated PTSD. It can resolve remote childhood traumas that predispose survivors to the disorder. Assisted by the guidance of a trained healer, the ingestion of ayahuasca provides individuals with the opportunity to reestablish limbic connections and revise pathological ones.

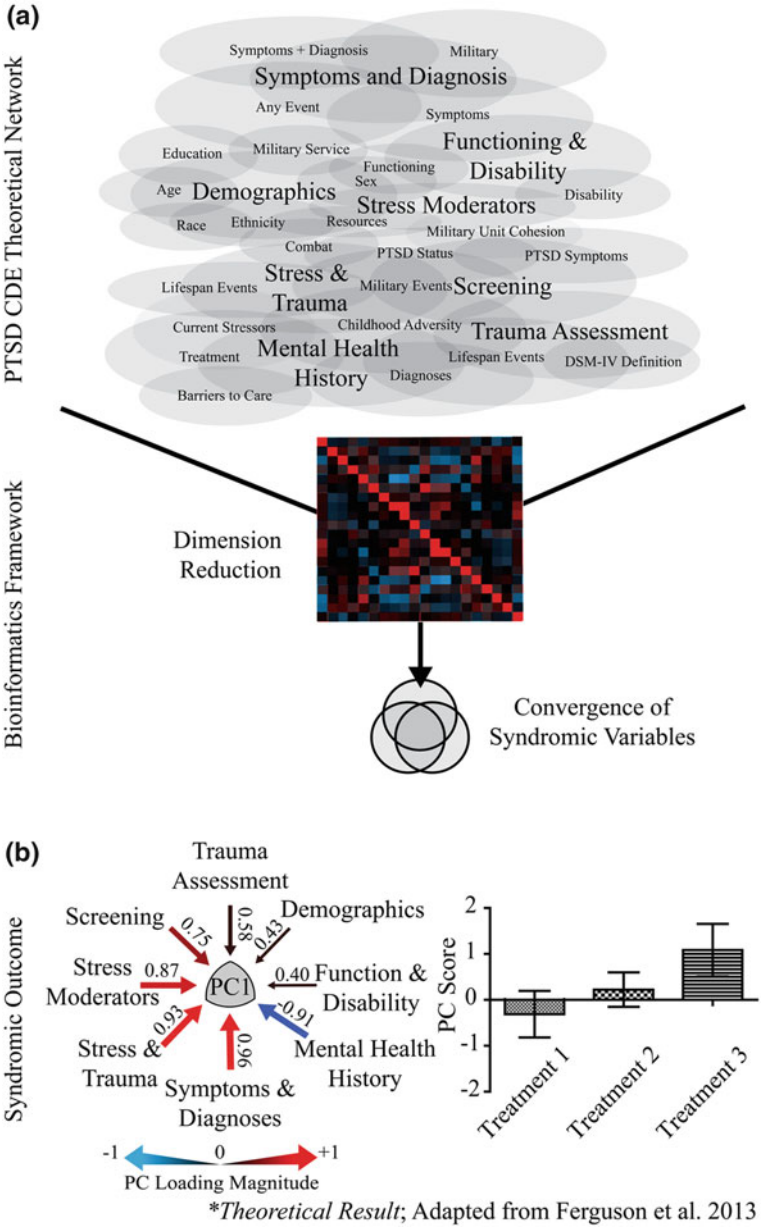
Ayahuasca facilitates healing by emphasizing emotions and sensations, thus it requires consideration of the mental state, and the physical and social environment. To prevent exacerbation of pathological symptoms, ayahuasca should be avoided in individuals with severe mental illness (in particular mania and psychosis), self-injurious behavior, or high suicidality. It is also imperative that therapeutic use of ayahuasca be in a well-supported and contained environment. As with exposure therapies, ayahuasca runs the risk of re-traumatization by introducing traumatic memories or triggers. An appropriate mind state and setting maximizes the individual's ability to look at each aspect of the self to resolve traumatic symptoms during their journeys. Individuals can then work toward a harmonious whole by integrating their ayahuasca experience into daily life.

A Paradigm Shift

What needs to be improved? Modern psychiatry is in a medical renaissance. Central to the current approach to psychiatry is Engel's biopsychosocial model, which suggests that illness and health are the result of an interaction between biological, psychological, and social dimensions (Engel 1977). The highly popularized field of integrative medicine is an expansion of Engel's model. Integrative medicine is a multidisciplinary approach that combines conventional treatments with alternative therapies. It uses the biopsychosocial model to look at each aspect of the self and move toward a harmonious whole. However, it also includes a critical piece missing in Engel's model: spirituality. Religion and spirituality have a significant impact on health behaviors, coping, physical and emotional symptoms, and quality of life. Ayahuasca has a tremendous therapeutic potential in this context, as its implementation weaves together all dimensions at the core of mental health: psychopharmacology, psychotherapy, psycho-education, psychosocial rehabilitation, and spirituality.

There are several barriers PTSD patients must grapple with on the road toward receiving the best treatment possible. One of these barriers is the stigma associated with having a mental disorder such as PTSD. Another barrier is that imposed upon the research community that is beginning to identify currently scheduled substances that are potentially beneficial for treating PTSD (Mithoefer et al. 2011, 2013; Oehen et al. 2013), yet are experiencing difficulty navigating research into scheduled substances (Dolan 2011). Researchers and clinicians should be allowed access, under the appropriate peer-reviewed protocols, to investigate the therapeutic potential of certain socially stigmatized substances like psychedelics. Substantial progress is being made regarding researchers' ability to explore these substances for their therapeutic potential, thanks to the hard work of the Multidisciplinary Association for Psychedelic Studies (MAPS) (Multidisciplinary Association for Psychedelic Studies 2013).

Yet another barrier touches at the very core of trying to diagnose PTSD using the current standardized diagnostic tool known as the DSM. The director of the National Institute of Mental Health (NIMH) recently stated that research into mental health should not be confined to the DSM categories, and that research should be steered toward finding better ways to diagnose mental health disorders from experimental research information (Ledford 2013). As a result, an NIMH strategy called the Research Domain Criteria Project (RDoC) was founded in 2009, aimed at promoting studies that will design novel methods for classification of mental disorders using metrics related to behavioral, genetic, neurobiological, and other potential mental health predictors (National Institute of Mental Health 2011). In line with this, a set of common data elements (CDEs) was defined in an attempt to standardize data collected in PTSD research (Kaloupek et al. 2010), which may prove useful in attempting to accurately diagnose and treat PTSD. Once we can properly diagnose PTSD, we can understand better how existing and experimental therapies will treat, and hopefully cure, PTSD.



Theoretical Result; Adapted from Ferguson et al. 2013

◂**Fig. 3.2** Theoretical syndromic framework to define the syndrome of PTSD, and how to test candidate treatments on this syndrome. Common data elements (CDE) have been developed to standardize data collection and interpretation for PTSD studies (Kaloupek et al. 2010). However, this large array of variables produces a complex matrix of correlations that may be difficult to analyze and interpret using conventional methods of analysis (**a**). By applying this type of data to our bioinformatics framework (Ferguson et al. 2013, 2011), we can leverage the correlation matrix for all variables in a PTSD drug trial, and apply pattern detection algorithms to reduce the dimensionality of this dataset to reveal new syndrome variables that describe the intersection between multiple variables simultaneously. Syndrome variables (**b**, PC1) can be defined as the collective contribution of multiple variables that contribute to a given amount of variance in the dataset. Each sub-variable loads onto their respective syndrome variable with the magnitude dictated by the correlation between that sub-variable and the entire syndrome variable. Posthoc testing of various predictor variables, including treatment categories, can then be tested on the syndrome variable to understand how these syndromic patterns move together as a response to treatments

Syndromic approach to PTSD. Although our current research at University of California San Francisco (UCSF) is not focused on psychiatric disorders per se, we are developing a novel approach known as syndromics (Ferguson et al. 2011) to better characterize and diagnose complex neurotrauma disorders like brain and spinal cord injury (Ferguson et al. 2013). This involves taking a data-driven, rather than hypothesis-driven, approach in order to more accurately assess existing and candidate therapeutic effects on complex syndromes of the nervous system, including PTSD. We hypothesize that by collecting and analyzing data using these criteria, and incorporating it into the bioinformatics framework we are developing (Ferguson et al. 2011, 2013), we will be able to identify the appropriate risk factors for PTSD, characterize the entire syndrome of PTSD, and more accurately test therapeutic efficacy in ongoing and future clinical trials (Fig. 3.2).

We propose that the notion of "set and setting," first coined by Leary in the 1960s, and specifically tested on the DMT experience (Leary 1966), applies to assessing the complex task of understanding and treating PTSD. While there may not be a universal treatment protocol for PTSD, there is a diverse framework of therapeutic avenues that can be tailored based on the multivariate nature of PTSD. This could include specific components in medical and personal history (set), as well as intentions for recovery and type of therapist and therapy that is administered (setting). The current diagnostic criteria for PTSD do not account for this complex constellation of symptoms, and the validity and usefulness of the current tools are being called into question (Ledford 2013). However, recent efforts have been made to harmonize and coordinate the information collected for patients with PTSD in an attempt to better characterize and treat it. These are known as common data elements (CDE), and are created by a consensus of clinicians and researchers in an attempt to standardize data collection for PTSD studies (Kaloupek et al. 2010). We aim to incorporate these standardized protocols of data collection specific for PTSD, and assess their role in the PTSD syndrome, and how they move together with respect to treatment (Fig. 3.2b).

Set and setting could be tested as predictor variables for therapeutic efficacy of existing and candidate therapies. This can take into account the mind state, intentions, and medical history of the patient, and variables involved in the administration of the therapy, such as location, ceremonial context, medicine, healer components, and integration methods can also be considered. The relevance of this has been shown in psychiatric research where questions were raised regarding the relative influence of the psychiatrist being a driving force in their patient's recovery, as opposed to the treatment alone. In fact, there was a substantial influence on recovery due to the method of administering the therapy (McKay et al. 2006).

Once the syndrome of PTSD is defined and subjects are reclassified based on their syndromic scores, simple univariate tests of predictor variables can be assessed. This can be used to screen risk/resilient factors for development of PTSD (Brewin et al. 2000), and test the therapeutic efficacy of emerging candidates for clinical trials (Mithoefer et al. 2011, 2013; Oehen et al. 2013; Thomas et al. 2013). These methods will enable us to not only better characterize the development of PTSD, but to identify potential risk factors to distinguish those that will be more susceptible to developing PTSD. The military may make use of this information to assign tasks to their soldiers, based on what will maximize their potential and reduce their harm. For example, in animal models of PTSD, pre-exposing subjects to escapable stress can prevent the development of LH behaviors (Petty et al. 1992). A famous example of this was observed following the 1976 kidnaping of 26 children who were kidnaped and buried alive (Terr 1990). Long-term follow-ups of these children revealed a high incidence of PTSD. However, one of the children who facilitated their escape in the face of death was not as traumatized by the event as the other children (Levine and Frederick 1997). He did not associate the experience with a sense of helplessness. He took action and freed himself and the rest of the children from their would-be grave. In doing so, he was able to have a cathartic response to the experience as it was happening.

By identifying these types of factors in a patient's medical and social history, we may be able to develop a more accurate framework to test therapies for PTSD, and potentially to steer certain individuals toward a lifestyle that will not lead to the development of PTSD in the first place.

Plans to apply syndromics to investigate ayahuasca for PTSD. (1) Build a database of previously published PTSD clinical trials, using syndromics to characterize which treatments are targeting the different components of PTSD; (2) Enrich this database with data from studies involving candidate therapies for PTSD, either specifically used for PTSD (e.g., the MDMA trials, mining data from healing centers treating PTSD with ayahuasca), or for other disorders (ayahuasca and ibogaine for addiction, psilocybin and LSD for end of life anxiety, among others); and (3) Conduct an observational study looking at ayahuasca for PTSD in different ceremonial contexts, combined with mining subjects' medical history to identify risk/resilience factors.

Concluding Remarks

DMT, the major psychoactive and possibly therapeutic component of ayahuasca, is currently classified as a Schedule I drug in the United States. According to the 2011 edition of the Drug Enforcement Administration (DEAs) resource guide on drugs of abuse, this class of drugs must meet the following criteria to be considered Schedule I under the Controlled Substances Act (see 21 USC para. 812): 1. High potential for abuse, 2. No currently accepted medical use in the US, and 3. Lack of accepted safety guidelines for use under medical supervision (United States, and United States Drug Enforcement Administration, Office of Chief Counsel 1996; Drug Enforcement Administration 2011).

As more research into psychedelics and marijuana is conducted (all of which are currently classified as Schedule I), these drugs will need to be reclassified if and when accepted therapeutic uses and treatment protocols are identified. The most promising example of this to date is the ongoing clinical trials with MDMA-assisted psychotherapy for PTSD. This has been shown to be safe and effective under supervised medical conditions (Mithoefer et al. 2011, 2013), and additional trials have been set up and published from international sites (Bouso et al. 2008; Oehen et al. 2013), and there are several ongoing and planned studies (MAPS 2013). We propose the same may be possible for the treatment of PTSD with ayahuasca, and aim to assess, using the syndromics approach, whether substances such as DMT can be considered for reclassification into the appropriate schedule based on their newly identified and accepted therapeutic potential and treatment protocols.

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