# N,N-Dimethyltryptamine: An endogenous neurotransmitter with extraordinary effects.

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In memoriam of Dr. Martha Blassnigg (\*08.09.1969; †27.09.2015) who went home much too soon.

#### **Abstract**

The most complex physical object in the known universe is the human brain and the most complex mental phenomenon is the human psyche. Humankind has travelled through outer space and we now possess detailed charts of the moon and many other extraterrestrial objects. However, hitherto modern science is unable to provide a comprehensive cartography of the varieties of human experience (Fisher, 1971), despite the efforts of the extraordinary Swiss depth psychologist Carl Gustav Jung who provided a rudimentary "skeletal" map of the psyche. Ergo, the great frontiers of 21st century science are internal and psychological and it should be psychologies primary focus to systematically chart these largely unexplored "antipodes of mind" - the "terra incognita" - as Aldous Huxley eloquently formulated it (Huxley, 1956, p.71). In this context, it has been effectively argued that the discovery of several unique psychoactive chemical substances is methodologically as important to the study of the mind as the invention of the microscope to progress in chemistry or the telescope to astronomy (Grof, 2000, p.297). This paper reviews a powerful endogenous psychoactive agent, N,N-Dimethyltryptamine (DMT, a structural analog of serotonin and melatonin), which catalyses unique and highly astonishing phenomenological experiences. An eclectic, interdisciplinary approach is adopted and DMTs pertinence for systematic research in psychology and neuroscience is discussed.

**Keywords** N,N-Dimethyltryptamine, 5-hydroxytryptamine, phytochemistry, cognition, perception, neuroscience, psychology.

#### Introduction

What is mind? No matter.
What is matter? Never mind.

—George Berkeley (1685-1753)

In this classic couplet, Bishop Berkeley concisely addressed the quintessential philosophical question concerning the fundamental relationship between mind and matter (note that he employs Cartesian dualistic terminology; i.e., res extensa vs. res cogitans).

The question Berkley poses is the following: Can mind/consciousness ultimately be explained in a purely materialistic framework (is "it" reducible to neurobiological mechanisms, molecules, atoms, etc. pp.)? Vice versa, the quote addresses the inverse question: Can the totality of physical reality (in Lockeian nomenclature, the entirety of "primary and secondary qualities") be accounted for solely in terms of mind? In other terms, is the material world an idealistic creation of the mind, as many ancient eastern metaphysical wisdom traditions postulate (experience, then, is the sole reality and the observer/subject and the observed/object are of identical nature; e.g., Bhagavad Gītā, Vedānta, Rigvedas, Yoga Sūtras of Patañjali)? This paradoxical conundrum is a deep-rooted perennial problem in the philosophy of mind and it has recently become a topic of interest for many neuroscientists.

## Neurochemistry of cognition

Contemporary materialistic reductionist neuroscience emanates from the provisional working hypothesis that the underpinnings of human cognition, perception, and consciousness are electrochemical. That is, electrical action potentials and chemical neurotransmission are hypothesized to ontologically cause these phenomena. However, it is possible that this unproven assumption might eventually turn out to be a case of epistemological naiveté. Nevertheless, it is an established scientific fact that there are certain classes

of material substances that affect consciousness reliably (the terms consciousness and mind are consequently used synonymously). However, not any arbitrary substance can alter the mind. The mind-altering substances in question have precisely defined molecular structures, which in turn cause very specific effects. For instance, there are certain psychoactive substances that induce sedation (for instance, Diazepam). This particular sedative is a specific case of a much larger chemical class (i.e., the Benzodiazepine family). Thus, there appears to be a systematic correlation between the chemical structure of certain compounds and the psychological effects they induce (in psychopharmacology this is known as the structure-activity relationship). Interestingly, especially from a neurochemistry/biology point of view, several naturally occurring secondary (possibly semiotic) plant compounds have close structural relationships with various mammalian (including human) neurotransmitters and can consequently bind to specific cell membrane receptors in the brain. Thereby, these chemicals can reliably change a variety of cognitive and perceptual processes (both quantitatively and qualitatively). N,N-Dimethyltryptamine (abbreviated as DMT) is a prototypical exemplar of such psychoactive chemicals (DMT has been oxymoronically referred to as "the spirit molecule"; but see Strassman, 2001). The receptor binding affinity of DMT is complex and hitherto only partially understood. However, it has been firmly established that DMT non-selectively agonises several members of the 5-HT<sub>2</sub> (5-hydroxytryptamin also known as Serotonin) receptor family (especially the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptor appear to be crucial for its psychoactive effects; but see McKenna et al., 1990; Aghajanian & Marek, 1999; Keiser et al., 2009). Except for the 5-HT<sub>3</sub> receptor, all 5-HT receptors achieve transmembrane signal transduction via the G-protein-coupled receptors. Recently, important fundamental research on the G protein-coupled receptor led to a series of Nobel Prizes (e.g., in 2000, 2004, and 2012).

Moreover, it has recently been demonstrated that DMT is an endogenous  $\sigma_1$  receptor regulator (Fontanilla et al., 2009;) and it has been hypothesized that it plays a mediative role in tissue protection, regeneration, and immunity (Frecska et al., 2013). From a chemical point of view, DMT is a prototypical representative member of the indolealkylamine family known as tryptamines. In its pure form, DMT is a white/clear, pungent-smelling,

crystalline solid. Its molecular structural geometry visualized in Figure 1 is closely related to Serotonin.

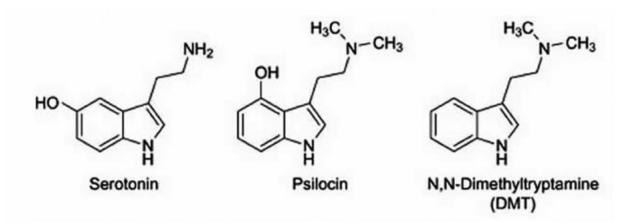


Figure 1. Compounds such as psilocin (synonymous with 4-hydroxy-N,N-dimethyltryptamine, a precursor of psilocybin which is also known as O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) and DMT (N,N-Dimethyltryptamine) have chemical structures that resemble the neurotransmitter serotonin (5-hydroxytryptamine). This structural similarity to serotonin allows them to stimulate serotonin-sensitive neurons. Note that the intermolecular serotonin motif is embedded in both structures.

From a phylogenetic perspective, DMT is an evolutionary very old molecule which is ubiquitously present in the plant and animal kingdom (Smith, 1977). In 1961, Nobel Prize laureate Julius Axelrod reported in the journal Science that the enzyme N-methyltransferase in a rabbit's lung is able to mediate the biotransformation of tryptamine into DMT (Axelrod, 1961). More recent converging evidence strongly suggests that DMT is an endogenous neurotransmitter in the human brain (e.g., Cozzi, et al., 2011; Fontanilla, et al., 2009; Cozzi, et al., 2009). Surprisingly, DMT is actively transported into the brain via the blood-brain-barrier (a process that is costly in energetic terms because it requires movement against the concentration gradient). This factum has been discovered by Japanese scientists 30 years ago (i.e., Yanai et al., 1986). Given that the brain in an extremely sensitive homeostatic organ, it constantly protects itself from toxins and undesired agents. Consequently, the blood-brain-barrier is highly selective and only very few essential compounds like glucose and other essential nutrients are actively moved across this membrane into the brains tissue. The phenomenon that DMT is actively transported across this protective barrier suggests that it plays a crucial role in ordinary brain metabolism. Moreover, DMT does not built up tolerance, as other psychoactive tryptamines do (no significant desensitisation after repeated administration; see Strassman & Qualls, 1994; Strassman et al., 1994) and it is quickly metabolised (consequently its duration of action is relatively short-lived). Again, this indicates that it is a natural building block of mammalian neurochemistry. At the moment, there is no explanation as to why mammals have evolved an endogenous neurotransmitter that is able to produce profoundly altered states of consciousness. From an evolutionary point of view one has to ask the question: What is the adaptive advantage of this compound in terms of survival or reproduction? However, given that the intracellular cascade triggered by DMT is not yet fully understood it seems very difficult to imagine that science is soon able to account for its much more intricate effects on perception and consciousness (the hard problem) from a quantitative point of view.

# DMTs qualitative phenomenology

From a psychological vantage point, DMT has very remarkable effects, too. One of DMTs most salient activity characteristics is that it affects visual perception in the most spectacular ways possibly imaginable. In addition, it profoundly changes the functioning of a multitude of core cognitive capacities. A brief (though incomplete) synopsis of DMTs subjective effects is summarised in the following list:

- Profound changes in sensory perception across modalities (e.g., perceptual distortions, vivid cross-modal hallucinations, visions, synaesthesia)
- Highly symmetric and oftentimes fractal multidimensional visual hallucinations of astonishing beauty and complexity
- Spectacular visual percepts (impossible objects which are essentially ineffable)
- Subjective experience of extrasensory perceptions (e.g., telepathic phenomena are commonly reported)
- Changes in time and space perception (e.g., time dilation, timelessness/ experience of infinity/eternity, limitlessness/omnipresence)
- Journey-like "breakthrough into hyperspace" (trans-dimensional travel into parallel dimension and contact with conscious "otherworldly hu-

- manoid beings" is commonly reported under high doses of DMT)
- Altered body image (e.g., out-of-body-experience, taking on an animal/alien body)
- Intense changes in mood (ranging across the whole spectrum of emotions from total serenity/bliss to extreme terror)
- Sense of profound meaning and deep spiritual insights (e.g., gnosis)
- Experience of very profound "mystical states"
- Dissolution of ego boundaries (e.g., ego-death, shared consciousness)
- Feelings of interconnectedness (e.g., communion with nature, monistic all-is-one experience)
- State of union and spontaneous realisation of oneness (nonduality, yoga)
- Near-death experience
- Experience of emptiness, nothingness, pure I-am-ness
- Feelings of tranquillity
- Being freed from one's body and becoming integrated with one's cosmic nature
- Feeling of sudden realisation of one's homogenous cosmic essence
- State of inner harmony (Samadhi)
- Experience of a transcendental reality
- Collapse of ego-ignorance phantom (dissolution of self-limitation)
- Transformation of self-perception, transmutation of entire being (self-transcendence)
- Expansion of awareness (experience of boundless primordial awareness)
- Experience of higher states of consciousness
- Feelings of awe and wonder
- Feeling of awakening from an illusion to a larger "more real" reality
- Appreciation of nature (perception of nature as animated and alive, biophilia)
- Sudden insights into the nature of self and the nature of reality (epiphany or "satori" like experience seeing into one's true nature)
- Access to unconscious "Jungian alchemical archetypal" information

#### Potential adverse effects

• Acute panic reaction (depending on idiosyncratic personality structure and situation)

- Substance induced psychosis (ICD-10 diagnosis code F16.5 low incidence rate)
- Hallucinogen persisting perception disorder (DSM-IV diagnosis code 292.89 – low incidence rate)

The following paragraphs reprint two experiences reported by research subjects who participated in Rick Strassmans early DMT which were conducted in Mexico in the 1990s.

"The trip started with an electric tingling in my body, and quickly the visual hallucinations arrived. Then I noticed five or six figures walking rapidly alongside me. They felt like helpers, fellow travelers. A humanoid male figure turned toward me, threw his right arm up toward the patchwork of bright colors, and asked, "How about this?" The kaleidoscopic patterns immediately became brighter and moved more rapidly. A second and then a third asked and did the same thing. At that point, I decided to go further, deeper. I immediately saw a bright yellow-white light directly in front of me. I chose to open to it. I was consumed by it and became part of it. There were no distinctions—no figures or lines, shadows or outlines. There was no body or anything inside or outside. I was devoid of self, of thought, of time, of space, of a sense of separateness or ego, or of anything but the white light. There are no symbols in my language that can begin to describe that sense of pure being, oneness, and ecstasy. There was a great sense of stillness and ecstasy." (excerpt taken from Strassman, 2001; p.244)

"Eight minutes into his non-blind high-dose injection, he described this encounter:

That was real strange. There were a lot of elves. They were prankish, ornery, maybe four of them appeared at the side of a stretch of interstate highway I travel regularly. They commanded the scene, it was their terrain! They were about my height. They held up placards, showing me these incredibly beautiful, complex, swirling geometric scenes in them. One of them made it impossible for me to move. There was no issue of control; they were totally in control. They wanted me to look! I heard a giggling sound - the elves laughing or talking at high-speed volume, chattering, twittering." (excerpt taken from Strassman, 2001, p. 188).

It should be noted that the phenomenological experiences reported under the influence of DMT are interindividually very heterogeneous (perhaps partially due to a combination of genetically coded neurotransmitter receptor polymorphisms and idiosyncratic psychological variables) and are contingent upon set and setting (that is, internal psychological and external situational factors play an important role). However, several phenomenologies are reliably induced across diverse subjects (e.g., complex visual hallucinations, out-of-body-experiences, trans-dimensional travels, etc.).

Space does not permit a detailed discussion of DMTs experiential phenomenology, particularly because linguistic expressions are circuitous and often largely inadequate in order to convey its diverse spectrum of psychological effects (ineffability is a defining hallmark of the translinguistic DMT ontology which reaches far beyond the bounds of human imagination). The perceptions and insights that are catalysed by this compound are often described as being at total invariance with the socially grounded models of contemporary western paradigms. Interestingly, several of DMTs structural analogues (e.g., Psilocybin, a compound which is present in the "magic" mushrooms which are endemic to the UK, Mantle & Waight, 1969; see also Figure 1) have phenomenologically comparable though not identical effects (cf. Hasler et al., 2004). However, hitherto the extraordinary cognitive changes triggered by DMT cannot be accounted for by any of the existing theoretical frameworks provided by neuroscience and psychology.

## Endogenous but prohibited

Despite the exceptional characteristics of DMT and its ubiquity in nature, many mainstream psychologists and even professional neuroscientists are utterly unaware of its existence (presumably, due to academic overspecialisation and the fact that the conventional neuroscience textbooks do not mention it at all, e.g., Gazzaniga & Mangun, 2014; Kolb & Whishaw, 2009). Furthermore, systematic and methodologically valid research is highly restricted due to the fact that DMT is classified as a "Class A drug" in the UK and similarly tightly regulated as a "Schedule I substance" in the US. This classification is clearly not evidence based and it inhibits scientific

progress and innovation (let alone the fact that it violates the principle of cognitive liberty, that is, the right to mental self-determination).

In this context, it is noteworthy that the Brazilian União do Vegetal (UDV - www.udv.org.br) was granted precedential legal permission to use a DMT containing drink (named Ayahuasca) in their ceremonies. The UDV, which is claiming roots as far back as the 10th century BC, utilises Ayahuasca in a program of spiritual evolution based on mental concentration and the search for self-knowledge. From a juridical point of view, it is very interesting that the US Supreme Court adjudicated in 2006 that the UDV is legally permitted to deploy Ayahuasca as a religious sacrament (under the protection of the "Religious Freedom Restoration Act").

# Ayahuasca: An ancient phytochemical synergy

From a much larger historical perspective, DMT has been utilized for spiritual/shamanistic rituals for millennia by several ancient cultural traditions. As mentioned before, it constitutes the active pharmacological principle in Ayahuasca, a plant based, drinkable concoction, which is traditionally used by indigenous tribes in the Amazonian rainforest for divinatory and healing purposes. In itself, DMT is orally inactive because the monoamine oxidase (MAO) system within the gastro-intestinal (GI) tract deaminates it. However, somehow the aboriginals have developed sophisticated intuitive knowledge concerning its combinatorial pharmacodynamics. In order to prevent DMTs decomposition in the gut, they mix it with a plant-based MAO inhibitor.

To be specific, the typical primary ingredients of the Ayahuasca brew consist of two plants, Psychotria Viridis (which contains the DMT) and Banisteriopsis Caapi (which contains the β-carboline harmala alkaloid designated as harmine). Harmine functions as a selective and reversible inhibitors of the enzyme monoamine oxidase A (MAO-A) that prevents the enzymatic breakdown of DMT in the GI-tract, thereby allowing it to be transported via the blood-brain barrier. Hence, it is the combination of these two plants, which enables DMT to become psychoactive. Quite thought-provokingly, the chemical literature labelled Harmine for some time as telepathine. This

chemical was so named because of the effects reported by Amazonian tribal members (e.g., telepathic communication, clairvoyance, precognition, psychic diagnosis, necromancy).

Western science has just relatively recently learned about DMT and its psychoactive effects from ethnophamacologists who were able to conserve this ancient cultural knowledge literally in the last minute because old shamanic traditions are being extinguished at a fast pace by the modern industrial world. The inhabitants of the Amazonian rainforest have a very close relationship with, what they call "plant-spirits". They regard Ayahuasca as a wise "plant teacher" which enables them to communicate with the "spirit world" (Beyer, 2009). It should be noted that in the shamanic paradigm the dichotomy between spiritual and medicinal is not clear-cut as the European heritage suggests and "sacred" plants play a central role in these traditional indigenous contexts.

Unfortunately, the Amazonian rainforests are currently being destroyed at a very alarming rate. The Amazonian biodiversity is among the richest in the world, although the number of species in the red list of the IUCN (International Union for Conservation of Nature) is growing steadily every year. The destruction of the natural environment goes hand in hand with the loss of culturally embedded ancient folk-knowledge concerning the utilisation of specific plants for medicinal and spiritual purposes. Moreover, younger generations are not very interested in the continuation of the Shamanic traditions of their predecessors. They prefer to move into modern technologized cities in order to take their place in the materialistic market economy and consequently thousands of years of accumulated and potentially highly valuable information is lost in this cultural transition.

### Conclusion

Brevity does not permit me to review many intriguing aspects of this multifaceted topic (e.g., DMTs relation to psychological conditioning/extinction, neurogenesis, neuroplasticity, psychoneuroindocrinology, psychoimmunology, epigenetics, and the neuroanatomical correlates of its effects). I could only try to provide a very rudimentary introduction to this fascinating newly emerging research domain. It should be emphasized that this subject (psychoactive plant compounds and human cognition, perception, and consciousness) is located at the cutting edge of modern cognitive neuroscience and psychology and it encompasses many other adjacent disciplines (e.g., physics, chemistry, botany, pharmacology, psychiatry, anthropology, history, archaeology, philosophy, religion, medicine, art, law, ethics, etc. pp.; cf. Bois-Mariage, 2002).). I am convinced that many researchers will develop a deep interest for this topic if they have not already done so.

For further information, the interested reader is referred to the book "DMT: The spirit molecule" by Rick Strassman (2001) who was the first to conduct FDA approved rigorous scientific human trials with DMT in the 1990s. His book provides a comprehensive synopsis of DMTs neurochemistry and its experiential phenomenology. Strassman hypothesized back in the 90s that DMT might be present in the human pineal gland. This hypothesis was largely ignored by the scientific community. However, his prediction has recently been partially corroborated. In 2013, researchers first reported the presence of DMT in rodent pineal gland microdialysate (Barker, et al., 2013). The pineal is a photoreceptive endocrine gland whose primarily known function is the regulation of the circadian rhythm via the secretion of melatonin (N-acetyl-5-methoxy tryptamine), another serotonergic member of the tryptamine family (but see Reiter, 1991). Because the photosensitive pinealocytes have a strong resemblance to the photoreceptor cells of the eye, the pineal gland has also been labelled as the "third parietal eye" (Eakin, 1973). It has been subject to much speculation since Claudius Galenus and later René Descartes who famously termed it the "principal seat of the soul".

#### Future research directions

To conclude, I would like to delineate some potentially fruitful directions for future research on DMT and formulate several empirically testable hypotheses:

DMT and its vastly more potent relatives (e.g., 5-methoxy-N,N-dimethyl-

tryptamine acronymized as 5-Meo-DMT) might lead to the discovery of new classes of neurotransmitter systems (cf. the discovery of the endocannabinoid system) that would deepen our understanding of basic neurochemistry and may ultimately lead to the design of new pharmacological agents in order to treat mental pathologies (cf. Jacob & Presti, 2005) or to enhance cognition (e.g., nootropics) or expand consciousness in the healthy population.

Another research agenda should focus the role of DMT and its relatives in molecular biology. The National Genome Research Institute published data that indicates that the costs of genetic sequencing (DNA micro arrays) are decreasing fast than Moore's law for computational performance predicts (http://genome.gov/sequencingcosts). This development opens up unprecedented large-scale analytic possibilities for the newly emerging discipline of neurogenetics. For example, in analogy to the genome, the proteome, and the connectome, the receptorome aims to map the total number of genes that code for receptors and receptor molecules in the brain. In this regard, it has recently been argued in a paper titled "Psychedelics and the Human Receptorome" that "it should be possible to use this diverse set of drugs (psychedelics) as probes into the roles played by the various receptor systems in the human mind" (Ray, 2010, p.1; content in bracket added).

The neurochemical correlates of the various meditative states of mind are another vibrant research topic. Researchers have observed statistically significant overlap between the neural correlates of mediation and psychedelic experiences. Consequently, there might be a significant degree of overlap between the neurochemical substrates of these altered states of mind. In this regards, the influence of DMT on microtubule (neuronal microstructures which form part of the cytoskeleton) should be a focal point of systematic scrutiny (but see Hameroff & Penrose, 2014).

Recent research provides evidence that DMT has psychoneuroendocrinological and psychoneuroimmunological effects (Frecska et al., 2023). Fascinatingly, it has been shown in a publication by Epel et al. in 2009 (co-authored by Nobel Prize laureate Elizabeth Blackburn) that mediation influences telomere length (an indicator of biological age). Given that

DMT and various related psychoactive tryptaminergic compounds induce states of mind that are partially qualitatively congruent with the mental states achieved by meditative practices it seems likely that the experiences triggered by DMT also have the potential to positively affect telomere length (e.g., via telomerase activity). Based on the assumption that DMT can induce robust longitudinal changes on various levels (physical and psychological) it seems likely that genetic changes are involved. Future research should focus on the (epi)genetic fundament of these changes (how gene methylation/transcription/ expression is altered following exposure to psychoactive substances).

Another line of research should investigate the interplay between quantum physical phenomena and altered states of consciousness. The theoretical framework of quantum physics ascribes a pivotal role to consciousness (e.g., Schrödinger's wave equation). Consequently, substances which profoundly change the main pillar of this theoretical tenet (that is, consciousness and the associated mechanics of perception) should be of significant interest to the physics community. The disciplines of physics and psychology should pursue a close interdisciplinary discourse and collaborations in order to combine their efforts and insights (this has happened before, for instance, the physicists Albert Einstein and Wolfgang Pauli were in close communication with depth-psychologist C.G. Jung).

Yet another auspicious line of research is an investigation of the effects of DMT on creative thinking and cognitive flexibility (i.e., DMT as a catalyst for creativity and innovation; cf. Frecska et al., 2012). Given that DMTs phenomenology deconstructs conventional orthodox cultural worldviews it has the potential to facilitate novel perspectives on multifarious philosophical questions and might even contribute to the resolution of "hard" scientific problems (cf. Willis, et al., 1966).

There is much more scientific virgin that soil awaits thorough investigation. A largely unexploited research area comprises of careful empirical tracings of the effects of various non-naturally occurring synthetic psychoactive tryptamines which have been developed by the pioneering chemist Alexan-

der Shulgin (see Shulgin & Shulgin, 1997). His work entails an extensive chemical toolbox for future work in neuroscience and psychology. In his book "TiHKAL - Tryptamines I have known and loved" he provides a detailed index of more than 50 psychedelic compounds (many developed by himself). The book entails a description of their synthesis, exact chemical structures, dosage recommendations, and qualitative comments. Most of these compounds have yet to be rigorously researched – a task for the next generation of curious and open-minded scientists. To provide an intriguing example, one of the tryptamines described by Shulgin is DiPT (Diisopropyltryptamine). It has unique properties because it does almost exclusively affect the auricular sense (i.e., nonlinear shifts in pitch perception - other sensory modalities remain largely unaffected). It is apparent that DiPT should be of keen interest to researchers trying to understand the neural basis of auditory perception. However, up until now systematic research has not been conducted (experimental ornithological studies of avian vocalisation/bioacoustics might be a fertile starting point).

Finally yet importantly, the experiences DMT evokes are of particular fascination to artists, for obviously reasons (e.g., Grey, 2012). Several visionary artists have been deeply inspired by their transcendental experiences with DMT and related compounds (see Figure 2).



Figure 2: The net of being by Alex Grey (inspired by the Mahayanian metaphor of Indra's net).
Further artworks created by Alex Grey are available under the following URL: http://alexgrey.com/art/

Finally, it remains an open question why DMT (and its structural relatives) are not part of the mainstream discourse in psychology and neuroscience. Especially given its apparently central role in perceptual processes, its pertinence for consciousness studies, its implications for understanding mood disorders and emotions in general, and its far-reaching philosophical implications? A Kuhnian paradigm shift is needed. The study of naturally occurring (plant derived) substances should be allowed into academia in order to foster the elucidation of the interplay between psychoactive chemicals, cognition, and consciousness.

Off the Lip: Science over politics!

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