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A Global Workspace, Evolution-Based Model of the Effect of Psychedelics on Consciousness

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We review data on the mental effects of psychedelics and their corresponding neurobiology to advance a model of consciousness based on the global neuronal workspace theory and an evolutionary perspective. Although some restrict the term *psychedelics* to certain serotonergic drugs, we opt for a broader definition. The term comprises five categories of substances: classical psychedelics, empathogens, cannabinergics, dissociatives, and deliriants. The neurobiological correlates of the perceptual and cognitive effects are discussed for each category. Finally, we consider the relevance of psychedelics for research on consciousness as well as for mental health.

Keywords: evolutionary perspective, psychedelics, altered states, global neuronal workspace, brain modules

The term *psychedelic* means "mind-manifesting" (Kaplan, 2016) and is here broadly defined in terms of substances that affect perception and cognition in a way that induces the experience of an altered state of consciousness. As the experience may feature hallucinations, these substances are occasionally referred to as hallucinogens.

Psychedelics are a subcategory of psychotropics, which includes all psychoactive substances. Our main objective is to explore substances that influence mental processes in a manner that induces significant changes in how people perceive themselves and the environment; including, but not limited to, delusions, paradoxical thinking, derealization, depersonalization, synesthesia, and radical alterations is the intensity and quality of perception. We focus on the following five categories of psychedelics and argue that they offer insight into the nature of consciousness: (a) Classical psychedelics include substances such as LSD, psilocybin, and mescaline that affect serotonergic neurotransmission and often produce profound changes in sensory perception and cognition (Nichols, 2016). (b) Empathogens are drugs such as MDMA that induce euphoria, empathy, and increased attentiveness—primarily by stimulating the release of serotonin—but typically exert more limited effects on sensory perception (Kamilar-Britt & Bedi, 2015). (c) Cannabinergics include substances that affect endocannabinoid signaling, typically by binding to cannabinoid (CB) receptors (Citti, Braghiroli, Vandelli, & Cannazza, 2018). The best described example is THC, the primary psychoactive compound of cannabis, which induces changes in perception, heightened mood, altered cognition,

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and impaired short-term memory. (d) Dissociatives are substances such as ketamine that cause depersonalization and derealization—particularly in the form of feeling disconnected from the environment, the body, and the sense of self—in addition to altered perception (Sassano-Higgins, Baron, Juarez, Esmaili, & Gold, 2016). (e) Deliriants, exemplified by hyoscine, are found in certain plants and mushrooms. They induce a state of delirium and produce effects similar to a delirious fever, characterized by confusion and an inability to control actions (Volgin et al., 2019). The categories are presented in Table 1 along with additional information.

The psychedelics appear to be relatively selective for conscious processes and exert limited overt effects on autonomic functions of the nervous system such as control of heart rate, smooth muscles, and cerebellum-controlled coordination of muscle movement (see references above). Psychedelics generally have limited toxicity, resulting in the relatively low incidence of morbidity and overdose mortality compared with other psychoactive substances such as alcohol, cocaine or heroin.

Although psychedelics instill a range of both positive and negative effects, we will focus on effects that users typically find desirable. Our focus should not be viewed as an attempt to discount valid reasons for not consuming psychedelics; for example, concerns about panic or other acute effects, as well as the lack of longitudinal research necessary to identify long-term risks (Elsey, 2017; Jungaberle et al., 2018). Any substance that radically changes the perception

Table 1
Commonly Used Psychedelics

Category	Examples	Primary action	Primary source[a]	Characteristic effects
Classical psychedelics	Psilocybin LSD ("acid") Mescaline DMT	5-HT_{2A} receptor agonist	Mushroom Synthetic Cactus Plant	Sensory distortion, hallucinations, lose sense of time, euphoria, synesthesia, empathy, derealization, depersonalization, oneness
Empathogens	MDMA ("ecstasy") AMT	Serotonin/monoamine release (inhibit reuptake or monoamine oxidases)	Synthetic Synthetic	Empathy, sociability, trust, sensory distortion, energized, euphoria
Cannabinergics	THC (in "hash" or "cannabis")	CB_1 receptor agonist	Plant	Sensory distortion, heightened mood, appetite, reduced short-term memory and attention
Dissociatives	Ketamine Nitrous oxide PCP ("angel dust") Salvinorin A	Antagonist of NMDA (glutamate) receptor κ-Opioid receptor agonist	Synthetic Synthetic Synthetic Plant	Detachment from surroundings, depersonalization, improved mood, hallucinations, anesthesia, analgesia, ataxia
Deliriants	Hyoscine Muscimol	Muscarinic acetylcholine receptor antagonist GABA receptor agonist	Plant Mushroom	Delusions/hallucinations, impaired attention, confusion, agitation, drowsiness

Note. AMT = α-methyltryptamine; GABA = γ-aminobutyric acid; CB = cannabinoid. The taxonomy is based on a combination of mental effects and neurobiological action. Both the taxonomy and the inclusion as a psychedelic is somewhat arbitrary. This is not a problem for the present text, which focuses on effects of psychotropics that can help us understand consciousness.
[a] Most substances are available in synthetic form.

of reality may induce anxiety due to the apparent loss of personal control.

We start by presenting a model of consciousness that is based on the global neuronal workspace theory (Dehaene, 2014), combined with an evolutionary perspective on consciousness (Grinde, 2018). To contextualize our discussion, we advance a brief evolutionary perspective on why psychedelics exist in nature and why humans/animals avoid or consume them. We then discuss prominent mental effects of psychedelics and what is known about their neuronal correlates in the context of the model of consciousness we advance. Finally, we comment on potential benefits of psychedelics for the study of consciousness and for improving mental health.

Background

A Model of Consciousness

According to the global neuronal workspace theory, conscious perception relies on a continuous and complex back-and-forth signaling in wide-ranging neural circuits within the corticothalamic complex (Dehaene, 2014). This complex, which includes basal ganglia, claustrum, thalamus, and the cortices, is here referred to as the workspace. Even in the absence of awareness, continuous more-or-less synchronized activity occurs within these circuits, but a sentient experience implies a distinct perturbation of the signaling in which rapid and unpredictable neuronal activity is superimposed on the synchronized, slow-wave resting state.

A moment of conscious experience presumably reflects increased activity in a particular (but probably vast) subset of the 20 billion neurons of the brain that reside outside the cerebellum. As the brain constantly creates new experiences, the subset of neurons in the workspace shifts continuously. In electroencephalography (EEG) studies, slow but strongly synchronized activity (delta and theta bands of high amplitude) is associated with the absence of conscious processing, as in the case of non-REM sleep; whereas the less synchronized, high-frequency signaling (beta or gamma bands of low amplitude) presumably reflects the activity associated with conscious "broadcasting" in the workspace (Butler, 2012). REM sleep displays high-frequency signaling and might be described as "broadcasting without anyone listening." There are similar EEG patterns in other mammals, and they are considered a marker of consciousness (Seth, Baars, & Edelman, 2005). Some scholars consider sleep, particularly REM sleep, to reflect a form of consciousness. We prefer the view represented by the medical tradition, which requires a person to be able to "accurately report" (e.g., in response to queries about a sensation or experience) to be considered conscious (Seth et al., 2005).

The observation that consciousness is regularly turned on or off on a diurnal basis implies the existence of a neuronal "switch." In fact, circuits in the reticular activating system of the brain stem contribute to activating or dampening arousal (Edlow et al., 2012; Steriade, 1996). Another, perhaps more consciousness specific, switch appears to reside in the intralaminar nuclei of the thalamus (Saalmann, 2014; Schiff, 2009).

The capacity for consciousness is one of many functions that evolution has added to the brain (Grinde, 2018). Activity that is not brought to conscious awareness can be referred to as unconscious, whereas the term *subconscious* may be used for the indistinct boundary between the conscious and the unconscious. Subconscious activity is reflected in the way desired information can suddenly pop up in the mind, in the phenomenon referred to as intuition, and in demonstrations of subliminal perception (Dehaene, 2014). Young (2018) has suggested that roughly 95% of the activity in the brain is unconscious.

Evolution added a wide range of functions, here referred to as modules, to the brain to promote survival and reproduction (Grinde, 2016; Nesse, 2000). Although the modules may rely on particular regions of the brain, they reflect activity in large and overlapping neuronal circuits. The conscious (awake) life, as experienced by a human, can be construed as a "consciousness module," which is typically turned on in the morning and off again at night.

The brain adds content to conscious experiences on a "need-to-know basis." In humans, the content may be subdivided into (a) information from external and internal sense organs; (b) feelings/emotions; and (c) other internally generated content such as thoughts, imagination, and memories. Evolution introduced additional modules in the brain for each type of input to

conscious experience, for example, a module for visual experiences, which can be subdivided into modules for adding color, movement, and contour. The process of generating conscious perception starts by filtering and adapting information in the unconscious brain. The various modules subsequently "compete" for the opportunity to broadcast their contribution in the workspace (Koch, 2012). Which contributions will be included, depend partly on unconscious processes and partly on conscious choice. For example, a person can decide to turn her head toward whatever she wishes to see, but she cannot easily turn off sounds reaching her ear.

This account can be analogized or visualized as the conscious experience being the surface on a sea of brain activity. Content rises from the deeper waters in the form of "bubbles" that, if they go all the way up, fuse together to form a unified, surface structure. The surface represents a moment of experience and includes all the elements that reached consciousness at that particular time. The bubbles, which constitute conscious content, are formed by modules operating in the unconscious sea of brain activity. They typically need 300 ms to reach the surface (Dehaene, 2014); starting, for example, when a visual image reaches the eye and ending when the image is presented to the perceiver. The time delay allows for the necessary processing, which reflects not only a selection of input, but also modifications and distortions of reality (Dehaene, 2014). The evolutionary rationale is not to create a high fidelity "film of life," but to present information in a way that optimizes conscious decision making for adaptive purposes. Abbott (2018) has referred to the brain as a "hallucinating engine" due to its capacity to distort reality, normally without the individual being aware of any distortion.

Evolution likely added feelings to improve the capacity for making behavioral choices (Grinde, 2018). The term *feelings* in this context encompasses any emotion or sensation that carries an element of being pleasant or unpleasant. The positive and negative aspects of feelings are meant to guide behavior toward what is good for the genes (i.e., optimizes probability of survival) and away from what is detrimental. For example, movement is incentivized toward a source of food and away from predators. It seems likely that feelings (in the present meaning) first evolved with the amniotes (reptiles, birds and mammals; Grinde, 2018).

The positive and negative elements of feelings can be described in terms of three distinct mood modules (Berridge & Kringelbach, 2015; Grinde, 2012a; Leknes & Tracey, 2008): Negative feelings rely on a single "pain," or unpleasant module; that is, whether it is relevant to social punishment (such as guilt) or to physical injury, the same neurological circuits deliver the negative component of the experience. The reward system, on the other hand, is divided into a seeking (or wanting) module, which is meant to stimulate the individual to seek opportunities and motivate action, and a liking module, which ensures that opportunities are consumed or utilized once present. The two modules are illustrated by the example of following the smell of a bakery and eating a cake, respectively. The above classification reflects both evolutionary theory and present knowledge regarding the underlying neurobiology. The primary function of feelings is to influence the organism, not vice versa, which explains why experiences like pain or fear are not easily turned off by sheer willpower and why feelings can influence decisions even when they are not recognized on a conscious basis (Tamietto & de Gelder, 2010).

To summarize, a conscious experience is based on at least two levels of brain activity. Unconscious activity prepares possible information for awareness followed by the actual broadcasting of select information. Both activities rely on neurotransmitter signaling and are subject to the influence of psychotropics.

The explanatory model of the effect of classical psychedelics on consciousness referred to as relaxed beliefs under psychedelics complements the present account (Carhart-Harris & Friston, 2019). This model is built on two theoretical interpretations regarding how the brain functions adaptively. The first is the free-energy principle, which is an attempt to describe the behavior of living systems in general. In short, living organisms are designed to resist disorder and minimize uncertainty to accomplish valued, positively valenced, and survival-oriented goals. The second, and somewhat related, entropic brain hypothesis, proposes that within a relevant boundary, the entropy of spontaneous brain activity reflects the richness of subjective experience.

According to this view, psychedelics acutely increase the overall entropy of brain activity, an effect the user describes as enhanced diversity and vividness of experiences. The change is proposed to reflect the increase in signal complexity, also referred to as desynchronization, which is typical for classical psychedelics (Muthukumaraswamy et al., 2013; Swanson, 2018). In other words, the increase in entropy of spontaneous brain activity is experienced as hallucinations and altered cognition. As the desynchronization can be measured (e.g., by EEG or magnetoencephalography), it is possible to investigate how it correlates with actual experiences during different types of altered consciousness. The relaxed beliefs under psychedelics model thus offers a neurological explanation for the effect of classical psychedelics based on level and openness of signaling.

Evolutionary Perspectives on the Use of Psychedelics

The recorded use of plants and mushrooms containing psychoactive substances dates back thousands of years (Merlin, 2003). The substances can be divided into two categories based on the motivation to consume them: (a) substances that directly activate brain reward circuits and thus promote positive feelings and (b) substances that activate the rewards in an indirect way, for example, by enhancing positive qualities of sensory percepts, by stimulating inquisitiveness, engaging spiritual feelings, or offering perceived insights. The first category seems to be relevant for all mammals (Siegel, 2005). The second category may not be unique to humans, but in our species evolution coupled brain rewards to a range of situations that animals likely care less about, such as spiritual pursuits and cognitive exploration (Grinde, 2012b).

Although a certain bias exists in our knowledge of psychotropics in that we tend to focus on substances that produce desirable experiences, this bias is not necessarily problematic. Any appreciable transformation of conscious experience can stimulate curiosity and thereby elicit rewards. Consequently, at least some people are likely to experiment with a consciousness altering substance as long as associated negative effects, such as nausea and anxiety, are not overwhelming.

Most psychotropics act by affecting (mimicking) neurotransmitters. More or less all animals with a nervous system use a set of key neurotransmitters, which includes the main neurotransmitters relevant for the present discussion: the monoamines (e.g., serotonin, dopamine, and norepinephrine), acetylcholine, glutamate, γ-aminobutyric acid (GABA), and endorphins (Chase & Koelle, 2007; Dyakonova, 2001; Fieber, 2019). The presence of psychedelics in plants that are desirable to humans may be due to these substances exerting an undesirable, and thus foraging deterring, effect on the nervous system of other vertebrate or invertebrate animals (Reynolds et al., 2018).

Mental and Neurobiological Effects

General Comments

The neurotransmitters that psychedelics resemble encompass a wide range of neuronal functions in both central and peripheral nervous systems. Many different proteins regulate their actions, including synaptic receptors, as well as proteins involved in reuptake, metabolism, and release of neurotransmitters. The genome typically codes for several subtypes of proteins for each of these functions. By binding to select proteins associated with a particular neurotransmitter, the psychedelics are afforded a degree of specificity regarding the neurological circuits affected.

The following five reasons explain why it is difficult to discern the precise neurobiological correlates of a particular psychedelic experience: (1) Our knowledge of the neurobiology is limited; (2) Most psychedelics bind to several proteins associated with a particular neurotransmitter; (3) Psychedelics may engage additional neurotransmitter systems directly or indirectly; (4) The neurotransmitter-modulating proteins are typically widespread across the brain; and (5) The experiences reported vary considerably not only among individuals, but even when the same person repeatedly ingests a particular substance. We consequently focus on key reported effects and neurobiological targets in the hope that the correlates they suggest inform how the brain operates.

Most of the effects experienced by ingesting psychedelics can also occur in the absence of chemical intervention, although the effect of the

drugs is likely to be extreme compared to what most people encounter in daily life. Drug-resembling experiences can reflect pathological conditions (e.g., schizophrenia, epilepsy, dementia) or arise in response to internal (e.g., hyperventilation) and external (e.g., sensory deprivation) triggers. In other words, the effects of psychedelics appear to be based on inherent attributes of how the brain operates, but they differ from the normal way the brain generates conscious content.

Classical Psychedelics

The most prominent feature of classical psychedelics is their profound effects on perception and cognition. Visual and auditory signals are not only distorted, but percepts, in the form of hallucinations, appear in the absence of external input. The primary target for these substances is to act as agonists on the 5-hydroxytryptamine(5-HT)$_{2A}$ receptor, but they can also interact with other serotonin receptors such as 5-HT$_{2C}$, and 5-HT$_{1A}$ (Nichols, 2016). Moreover, the activation of serotonergic circuits has downstream repercussions on key neurotransmitters such as glutamate, GABA, and dopamine (Canal, 2018; Vollenweider & Geyer, 2001). The observation that 5-HT$_{2A}$ receptor antagonists block at least the more prominent effects of classical psychedelics, substantiates the notion that this receptor serves an integral role in inducing the alterations in consciousness (Deco et al., 2018; Vollenweider, Vollenweider-Scherpenhuyzen, Bäbler, Vogel, & Hell, 1998). People suffering from psychosis may report experiences similar to those induced by psychedelics, and the 5-HT$_{2A}$ receptor is also a target for antipsychotics (Meltzer & Massey, 2011), further validating the core role of this receptor.

Various lines of evidence, including brain imaging and animal studies, suggest that the primary site of action is the prefrontal cortex, although other sites of action may include the basal ganglia, cingulate cortex, claustrum, and thalamus (Béïque, Imad, Mladenovic, Gingrich, & Andrade, 2007; Canal, 2018; Riba et al., 2006). The 5-HT$_{2A}$ receptors expressed on apical dendrites of neocortical pyramidal cells in prefrontal cortex layer V seem to be particularly relevant (Nichols, 2016). These neurons are well connected to subcortical regions, and their function in the broadcasting process may be to facilitate the selection and integration of elements to be broadcasted (Barkai & Hasselmo, 1994). The selection process has been referred to as gating (Cromwell, Mears, Wan, & Boutros, 2008). In the present terminology, it could be described as selecting which bubbles are allowed to proceed all the way to the surface of consciousness.

Crick and Koch (2005) have proposed that the claustrum, a thin sheet layered between the cortex and subcortical regions, plays a vital role in the selection procedure. The claustrum has a particularly high concentration of 5-HT$_{2A}$ receptors and is thus a likely target (Nichols, 2016). The claustrum has also been implicated in the perception of time (Yin, Terhune, Smythies, & Meck, 2016), which is noteworthy insofar as a striking effect of classical psychedelics is an altered sense of time (Heimann, 1994).

The brain is not designed to broadcast an exact representation of what the senses pick up. Chemicals acting on key circuits involved in broadcasting would be expected to further distort the experience. The activation of 5-HT$_{2A}$ receptors by classical psychedelics may cause this distortion by intervening in the selection, and perhaps "surface-integration," of bubbles. That is, the experience becomes scrambled and distorted, conceivably due to the opening of the gates for "aberrant" bubbles, for too many bubbles, or by not allowing the bubbles to form a coherent surface. The neurobiological correlate of this process may involve the activation of subsets of circuits in the workspace that do not correspond to any actual perceptual experience, or to the activation of many subsets of circuits simultaneously. Notably, classical psychedelics tend to reduce the oscillatory power in the cortex; that is, they decrease EEG amplitudes due to desynchronization (Swanson, 2018), which may reflect a more intense form of broadcasting as might be expected if the selection process was hampered.

The default mode network is situated (at least primarily) within the workspace and is associated with "mind wandering" and a preoccupation with internally directed cognition (Raichle, 2015). The default mode network typically displays reduced activity under the influence of classical psychedelics (Swanson, 2018), perhaps because the broadcasting of (pseudo)sen-

sory information is intensified. The shift of focus away from mind wandering to sensory conscious content may help to explain why the brain considers hallucinations to be external in origin, even though they can be generated in the absence of any external influence.

Classical psychedelics produce not only overt hallucinations, but also synesthesia (the crossover of sensory experiences such as seeing sounds or hearing colors), the main difference being that in cases of synesthesia, a particular sensory trigger can be identified, which is not the case for hallucinations (Brogaard, 2013). People who experience synesthesia in the absence of drugs typically report an enduring binding of a certain stimulus to a certain effect; for example, the letter A may consistently be perceived as red. Synesthesia induced by psychedelics is not fixed in a similar way. Synesthesia is linked to an increase in serotonergic and glutamatergic activity, whether it is induced by drugs, reflects a developmental trait, or is caused by brain injury (Brogaard, 2013). Brang and Ramachandran (2008) suggested that 5-HT_{2A} receptor activity is responsible for synesthesia, indicating that the mechanism driving this phenomenon is similar to that of hallucinations produced by classical psychedelics.

People who ingest classical psychedelics commonly report a lack of mental control (Dittrich, 1998), an experience that is likely the consequence of ingesting drugs that disrupt normal broadcasting and flood the mind with novel experiences. In doing so, the chemicals presumably interfere with the ability of the conscious brain to direct attention. Moreover, the prefrontal cortex is a main target of these drugs, and it may be relevant that this part of the brain also is implicated in decision-making and executive control (Domenech & Koechlin, 2015). Executive control includes the conscious-driven aspect of deciding what information the unconscious brain should incorporate in the broadcast.

A striking quality of classical psychedelics, compared with most other psychotropics, is that their effects are unpredictable and vary with a range of factors such as the amount ingested, personality, mood, expectations, and environmental conditions. For example, LSD users refer to their intoxication as "trips" and to adverse or unpleasant experiences as "bad trips." Prior to ingestion, it is not certain what direction the journey will take. The unpredictability of responses substantiates the notion that these substances disturb broadcasting, rather than exert their effect on lower levels of processing. By disturbing the broadcasting, the experience is expected to depend on whatever modules happen to be engaged at the time. If the fear module is already engaged, the effect may be to enhance and distort the bubbles coming from this module, which could then qualify as a bad trip.

During hallucinations induced by classical psychedelics, the processing center for visual stimuli in the occipital lobe is activated even when the eyes are closed (Swanson, 2018). This observation suggests that circuits in the occipital lobe are involved in both preparing information for broadcasting and in the actual broadcasting of information.

Epileptic seizures localized in either the left or the right occipital lobe typically induce visual distortions or hallucinations that are perceived as part of the visual field on the opposite side of the seizure focus (Panayiotopoulos, 2007), suggesting that the effect is on the module responsible for processing visual perception. If broadcasting had been affected, one would expect the experience to appear as emanating from both eyes. Seizures in the temporal or parietal lobes, however, can produce complex hallucinations that typically cover both visual fields (Panayiotopoulos, 2007), which is more like the effect of classical psychedelics. These observations substantiate the idea that changes in either the processing module (the occipital lobe) or the broadcasting procedure (temporal and parietal lobes) can distort the experience, but in ways that differ due to the different roles these brain regions play.

Empathogens

Empathogens, including the most studied substance MDMA, stimulate social connection by enhancing empathy and trust; they are also energizing, improve mood, and produce sensory distortions or mild hallucinations (Kamilar-Britt & Bedi, 2015). The latter effects of empathogens are somewhat similar to stimulants such as amphetamine (Rasmussen, 2008). However, typical stimulants are thought to exert their effects via the release of dopamine and norepinephrine, whereas MDMA is primarily serotonergic; that is, the drug preferentially increases the release and inhibits the reuptake of sero-

tonin, with lesser effects on norepinephrine and only a limited, indirect effect on dopamine (Berry, Gainetdinov, Hoener, & Shahid, 2017; Bershad et al., 2016). The positive effect on mood seems to be partly due to activation of 5-HT_{2A} signaling (van Wel et al., 2012). Sensory distortions probably involve the same receptor, which is engaged by classical psychedelics as well.

The impact on social relations is the most interesting aspect of empathogens. It is tempting to suggest that this effect reflects enhanced activity in modules responsible for gregariousness and compassion. The impact is not restricted to actually being present in a social setting, as MDMA also enhances self-regard and self-compassion, but the socializing effect is, nevertheless, optimized in the presence of friends (Baggott et al., 2016; Kamboj et al., 2015). Thus, the connection between social interactions and MDMA is reciprocal; the drug can enrich social interactions and, in turn, the rewarding effects of the drug are enhanced by the presence of others (Bershad et al., 2016).

MDMA increases oxytocin, and to some extent vasopressin, as an indirect consequence of its serotonergic effect (Dumont et al., 2009; Thompson, Callaghan, Hunt, Cornish, & McGregor, 2007). These neuropeptides are key players in regulating social relations and are likely, at least partly, to mediate the prosocial effect. In support of this notion, Bershad et al. (2016) have shown that the sociable effect of MDMA depends on the genetic type of the oxytocin receptor. Individuals homozygous for the A allele did not report enhanced sociability, unlike G allele carriers. Further research with empathogens may help us understand brain modules associated with interpersonal relations.

Cannabinergics

The desirable effects of THC include changes in perception and cognition, heightened mood, and increased appetite, whereas less desirable changes are reduced short-term memory and impaired motor skills and attention (Citti et al., 2018). The endocannabinoid neurotransmitters, which THC and related substances mimic, are typically released upon depolarization of neurons (Elphick & Egertová, 2001). The neurotransmitters then bind to CB receptors, particularly CB_1 receptors, on presynaptic glutamatergic and GABAergic neurons, causing a decrease in the release of, respectively, glutamate and GABA. Limiting the presence of glutamate results in reduced neuronal excitation, while limiting the presence of GABA enhances excitation by suppressing inhibition.

The CB_1 receptors are widespread in the brain, occurring at variable concentrations all over the corticothalamic complex (Pagotto, Marsicano, Cota, Lutz, & Pasquali, 2006). The typical effects of THC are thought to be a consequence of agonist binding to CB_1 receptors (Colizzi, McGuire, Pertwee, & Bhattacharyya, 2016). This assumption is substantiated by the observation that rimonabant, a CB_1 receptor antagonist, tends to block THC action (Justinova et al., 2008). Positive mood effects may be due to a downstream increase in dopamine release (Oleson & Cheer, 2012), as dopamine is involved in the seeking reward module (Kringelbach & Berridge, 2009). It is more difficult to suggest specific correlates for the effects of THC on cognition and perception. Still, the common occurrence of CB_1 receptors within the workspace is probably responsible for these effects, which suggests that the endocannabinoids are involved in the broadcasting process.

Dissociatives

One unique attribute of dissociatives, such as ketamine and PCP, is their capacity to reliably produce a sense of detachment from the immediate situation or environment (Sassano-Higgins et al., 2016). The external world is perceived as dreamlike or unreal. The detachment can also include depersonalization, which involves feeling detached from one's body or sense of self: The individual is able to observe his or her actions, but does not feel responsible for, or in control of, the actions. Looking in a mirror, the subject may fail to recognize whose image is reflected, while maintaining rational awareness as to the identity of the onlooker. Dissociatives can also distort sensory perception and produce hallucinations. Higher doses lead to complete loss of consciousness, as when used in anesthesia.

The out-of-body experience is analogous to the deficit in self-awareness present in people diagnosed with anosognosia or depersonalization disorder (Sierra & Berrios, 2001). Certain regions of the cortex, within the frontal, tempo-

ral and parietal lobes of the right hemisphere, are often damaged in individuals with anosognosia (Vuilleumier, 2004). Interestingly, an out-of-body experience can also be induced by stimulating the brain with electrodes applied to the border area between the parietal and temporal lobes (Blanke & Arzy, 2005; De Ridder, Van Laere, Dupont, Menovsky, & Van de Heyning, 2007).

Ketamine and PCP bind as antagonists on the NMDA type of glutamate receptor (Kamilar-Britt & Bedi, 2015). Glutamate is the most abundant excitatory neurotransmitter, and the NMDA receptors are widespread in the brain. Antagonists at this receptor are expected to decrease neuronal activity, which may explain the analgesic and cataleptic effects when used in higher doses. Based on MRI data, ketamine affects activity in both cortical and subcortical parts of the brain; however, the reported feeling of dissociation corresponds more specifically to an area on the inner part of the cortex where the frontal and parietal lobes meet (Stone et al., 2015). This location is in reasonable agreement with the information discussed in the previous paragraph, substantiating that the area is important for a module that generates self-awareness.

Users of classical psychedelics typically report a feeling of "unity," "ego dissolution," or "oneness with all" (Swanson, 2018). These descriptions appear to be related to the experience of dissociation engendered by ketamine, but may depend on a different neurobiological correlate. While the ketamine effect presumably reflects an inhibition of NMDA receptors in the parietal-temporal border region, the classical psychedelics may engender ego dissolution as a consequence of their capacity to disrupt broadcasting. If a person fails to recognize present experiences as related to those experienced before, the conclusion might be that the experiences are not stemming from his or her brain.

Salvinorin A, which is obtained from the plant *Salvia divinorum*, exerts both hallucinogenic and dissociative effects. The substance is primarily a potent κ-opioid agonist (Roth et al., 2002), and based on coadministration of relevant antagonists, the psychotropic effect appears to rely on κ-opioid receptors (Maqueda et al., 2016; Zhang, Butelman, Schlussman, Ho, & Kreek, 2005). Like other κ-opioid agonists, salvinorin A causes sedation and anhedonia, but it also produces symptoms of psychosis, including delusions (Butelman & Kreek, 2015).

The above discussion suggests the existence of a brain module designed to create a sense of self, and that this module helps to distinguish one's body from the surroundings. The corresponding neural circuits are likely localized within the frontal, temporal, and parietal lobes, and the glutamatergic NMDA receptors serve a key role in maintaining relevant activity. The effect of salvinorin A suggests that κ-opioid receptors are also involved; in fact, ketamine binds weakly to these (and other) opioid receptors (Smith et al., 1987). One may hypothesize that disturbances of this module, rather than broadcasting, is responsible for the dissociative effect of these substances.

Deliriants

Delirium implies a state of confusion that may include hallucinations, memory impairment, cognitive deficits, restlessness, and agitation. This state is common in psychosis and other mental disorders, but can also be evoked by deliriants (Volgin et al., 2019). The affective and cognitive effects of deliriants are less well studied compared with other psychedelics. Although there are several examples of the use of deliriants for recreational purposes, they are generally regarded as noxious, as the state of delirium or confusion is not particularly pleasant.

Compounds that induce delirium are found in a number of plants and mushrooms. Plants in the nightshade family contain hyoscine (also referred to as scopolamine), nutmeg contains myristicin, belladonna contains atropine, and fly agaric mushroom contains muscimol. Several of these substances have a history of medical use. One of the best studied deliriants, hyoscine, was originally developed for treating motion sickness. Typical deliriants are anticholinergics in that they act as antagonists of the muscarinic type of acetylcholine receptors, although some, like muscimol, are GABA receptor agonists (Volgin et al., 2019).

The more pronounced effects of deliriants are likely to reflect activity in subcortical parts of the brain (Volgin et al., 2019) and may be due to an imbalance of dopaminergic stimulation in the mesolimbic system as a consequence of impaired muscarinic receptors (Trzepacz,

2000). It is not clear what causes the hallucinogenic effect, but it may be due to a general disturbance of brain activity. Perhaps the hallucinations occurring in various mental disorders reflect similar disturbances. That is, the hallucinations do not require specific action on particular neurotransmitter systems; a more general dysfunction may similarly derail normal experiences. In line with this notion, derailed experiences are also observed as a consequence of strokes (Stangeland, Orgeta, & Bell, 2018) and epileptic seizures (Wheless, Willmore, & Brumback, 2009).

Discussion and Conclusion

Relevance for the Study of Consciousness

In the present model, we distinguish between modules that prepare information for broadcasting and the actual broadcasting required for information to reach consciousness. Substances that affect either or both of these processes are expected to change what a person experiences, and may thus help us understand the underlying neurobiological activity and consciousness more generally.

Researchers have suggested that psychedelics enhance or alter consciousness by restraining a gating mechanism that filters which elements are to be broadcasted (Bayne & Carter, 2018; Swanson, 2018). The apparent enhancement of consciousness may be due to both a reduction in filtering, stimulating a flood of conscious content, and to the unique and novel quality of the experiences produced. In the present terms, it may be a matter of both more bubbles rising to the surface and their "distorted shape." The notion of "altered states of consciousness" may simply reflect that the experience is overwhelming and novel, not that psychedelics create a fundamentally different, or enhanced, state of mind. In line with this interpretation, ketamine (in subanesthetic doses) increases signal diversity (or complexity) of spontaneous EEG, but this effect of ketamine is not evidenced in EEG evoked by transcranial magnetic stimulation (Farnes, Juel, Nilsen, Romundstad, & Storm, 2019). Transcranial magnetic stimulation–evoked complexity of EEG is used to probe the level of consciousness—meaning the degree of arousal or wakefulness, which suggests that ketamine alters conscious content rather than level of consciousness.

Another line of thought is that psychedelics foster insight and improve creativity by enhancing divergent thinking and problem solving (Harman, McKim, Mogar, Fadiman, & Stolaroff, 1966; Sweat, Bates, & Hendricks, 2016). Flooding the mind with unique experiences appears to be conducive to novel thoughts and thereby creative solutions (Frecska, Móré, Vargha, & Luna, 2012), even when working memory and directed attention are temporarily impaired. On the other hand, researchers have suggested that psychedelics do not improve the capacity to distinguish "real" insight from simply a feeling that one's thoughts are more profound or creative (Bayne & Carter, 2018).

Perhaps the effect of psychedelics ought to be demystified. They seem to be best described as agents that act on either modules designed to deliver conscious content or the process of conscious broadcasting. As such, they have considerable potential to improve our understanding of the brain, but the primary source of increased knowledge will likely come through scientific explorations rather than introspection. Future lines of investigation should include experiments that elucidate the detailed neurobiological effects of the various psychedelic substances reviewed and how these effects correlate with subjective experiences in humans and observable changes in animals.

Relevance for Mental Health

Compared to other animals, the human brain may be particularly malleable, as reflected in the importance of learning for our species and the observation that human infants require more time to reach maturity. That is, we probably rely more on brain plasticity than other species. Feelings, in the form of good or bad experiences, are meant to guide the process of learning (and adaptation to the environment) by labeling situations as desirable or undesirable for future reference and decision making. Thus, a strong emotional impact will tend to exert a relatively enduring effect on the mind. A bad trip may come back and haunt the person, whereas a good trip should predictably elevate mood. To the extent that one can increase the probability that the hallucinogenic experience is positive, for example, by creating a conducive

setting in appropriately screened and prepared individuals, these substances would be expected to possess a therapeutic potential. Ketamine, psilocybin, ayahuasca, and MDMA have already proven useful in treating conditions including depression, anxiety, and addiction (Carhart-Harris et al., 2017; Dos Santos et al., 2016; Mathew, Mathew, & Zarate, Jr., 2016).

If the aim is to enhance mood, one might ask why substances like heroin and cocaine, which directly activate the reward modules, are not considered preferable therapeutic agents. The problem is that such direct activation engenders both the potential for addiction and down-regulation of positive experiences. Moreover, the positive mood created by heroin and cocaine tends to rebound or devolve into a negative state as the drugs dissipate from the brain. Accordingly, the indirect way of activating rewards, as in the case of psychedelics, offers advantages. The brain is designed to develop through experiences. In other words, the reward modules are properly exercised by what is perceived as a "learning" event, not by direct hits or stimulation as delivered via heroin and cocaine.

The importance of learning implies that any novel situation may instigate a reward. Sensory stimuli, such as sights (Grinde, 1996) and sounds (Grinde, 2000), can also be rewarding. Boosting the complexity, novelty, or vividness of these stimuli is likely to enhance pleasure. Indeed, psychedelic users often report deep appreciation of musical sounds, regardless of whether the perceived sound is based on sensory input or on hallucinations (Zentner, Grandjean, & Scherer, 2008).

As with any medication, therapeutic use depends on whether the positive effects outweigh possible negative side effects. In the case of psychedelics, the cost-benefit balance is particularly difficult to predict as the outcome also depends on the "mental set" of the patient—the expectancies of the consumer and the state of mind in which the substance is taken. Feelings of security and a relaxed state of surrender are important elements that facilitate a profound and positive experience (Russ, Carhart-Harris, Maruyama, & Elliott, 2019). As expected, the perceived intensity of the experience correlates with long-term effects on mental health (Nichols, 2016). The more the experience diverges from any previous experience, the more profound and intense the person is likely to consider it to be. Many users report that these substances induced the most meaningful event in their lives (Griffiths, Richards, Johnson, McCann, & Jesse, 2008). Moreover, the positive effect typically lingers after the acute psychedelic experience (and the pharmacologic activity of the drug) has subsided—a phenomenon referred to as afterglow—which may facilitate the therapeutic effect (Majić, Schmidt, & Gallinat, 2015).

Any positive experience may improve mental health, but the therapeutic potential of psychedelics seems to go beyond what one would expect to achieve merely by activating reward modules. We shall briefly discuss some additional factors that may help explain this assertion.

Some substances, including ketamine, enhance brain plasticity, which has given rise to the term psychoplastogens (Olson, 2018). The effect on plasticity is presumably related to the role of glutamate in general (Naughton, Clarke, O'Leary, Cryan, & Dinan, 2014), and the NMDA receptor in particular (Li & Tsien, 2009), in controlling synaptic plasticity and memory. The induction of neuroplasticity, combined with stimulating strong and pleasant emotions, may help explain the relatively long-term positive outcome in patients with mood disorders. The positive feeling is associated with NMDA-receptor-dependent inhibition of activity in the lateral habenula—an area of the brain associated with "anti-reward" (perhaps better designated as "low mood") activity (Yang et al., 2018).

The dissociative effect, which is not limited to dissociative psychedelics such as ketamine, may imply an additional advantage in that the dissociation can disrupt or inhibit negative rumination. MDMA, for example, allows the patient to disconnect from traumatic memories in a process referred to as memory reconsolidation and fear extinction (Feduccia & Mithoefer, 2018). A related argument is connected with the ego dissolving effect of psychedelics. The advantage of ego dissolution is presumably that the patient mitigates or eliminates ingrained patterns of thought and dysfunctional habits, such as addictions and negative rumination. In the case of MDMA, trust in the therapist afforded by the empathogenic effect may enhance therapeutic value.

Facilitating compassion is a twofold way of improving happiness: (a) social relations offer strong rewards in enhancing positive feelings (Grinde, 2009), and (b) an empathetic person will tend to socialize more, thus initiating a spiral of good feelings. This effect is not restricted to empathogens, as classical psychedelics also enhance sociability (Nichols, 2016).

Many people report that psychedelics engender religious or mystical experiences (Johnson, Hendricks, Barrett, & Griffiths, 2019). In fact, numerous cultures have independently used natural psychedelics for spiritual purposes (Merlin, 2003; Schultes, Hofmann, & Rätsch, 2001). An innate tendency or proclivity for religiosity (Grinde, 2010), which is enhanced by the way psychedelics produce a sense of ego dissolution and "oneness with all" (Letheby & Gerrans, 2017), would help to explain why people so eagerly consider the strange effect of psychedelics to be imbued with spiritual significance (Johnson et al., 2019).

Experiences that cater to spiritual tendencies are expected to be positive, as connecting with spirits or gods offers rewards (Grinde, 2005). Moreover, associating the effect of psychedelics with religious ideas implies a connection that makes the experience more enduring, that is, more robustly integrated in the mind, thus reinforcing the positive effect. Finally, the religious setting combines the positive experience with the presence of a supportive social group. The apparent success of the Santo Daime religion in improving mental health presumably relies on this principle (Palhano-Fontes et al., 2019), as adherents use the ayahuasca brew as a sacrament. The brew contains DMT, which is considered a classical psychedelic.

A relevant question is whether the psychedelics can also improve life for those who do not suffer from a particular disorder. The betterment of otherwise healthy people is congruent with the World Health Organization's definition of health as a state of complete physical, mental and social well-being, and not merely the absence of disease. All drugs with a history of recreational use can, at least in some people under some circumstances, activate the reward modules of the brain; otherwise they would not have been desired and consumed. The pertinent issue is whether the benefits of taking psychedelic substances outweigh the pitfalls associated with their use, particularly as considered in a lifetime perspective. It is difficult to find a definitive answer to this question, not the least because the impact of psychedelics differs among individuals. Yet, we believe that the answer is more likely tilted toward the positive in the case of psychedelics compared with other psychotropic substances such as heroin, cocaine, tobacco, and alcohol. That is, moderate use of psychedelics may offer the average user more benefits than harm in the pursuit of happiness. Society, and indirectly members of that society, could gain further benefits due to the positive effects of some of these substances on compassion and sociability. In fact, researchers have associated the lifetime use of classical psychedelics with both positive mental health and prosocial outcomes (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015; Johansen & Krebs, 2015; Johnson et al., 2019), although carefully conducted cross-sectional and longitudinal studies are necessary to assess the validity and reliability of these findings and the theoretical framework advanced in this essay.

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