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Current Perspectives

The mechanistic divide in psychedelic neuroscience: An unbridgeable gap?

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ABSTRACT

In recent years, psychedelics have generated considerable excitement and interest as potential novel therapeutics for an array of conditions, with the most advanced evidence base in the treatment of certain severe and/or treatment-resistant psychiatric disorders. An array of clinical and pre-clinical evidence has informed our current understanding of how psychedelics produce profound alterations in consciousness. Mechanisms of psychedelic action include receptor binding and downstream cellular and transcriptional pathways, with long-term impacts on brain structure and function—from the level of single neurons to large-scale circuits. In this perspective, we first briefly review and synthesize separate lines of research on potential mechanistic processes underlying the acute and long-term effects of psychedelic compounds, with a particular emphasis on highlighting current theoretical models of psychedelic drug action and their relationships to therapeutic benefits for psychiatric and brain-based disorders. We then highlight an existing area of ongoing controversy we argue is directly informed by theoretical models originating from disparate levels of inquiry, and we ultimately converge on the notion that bridging the current chasm in explanatory models of psychedelic drug action across levels of inquiry (molecular, cellular, circuit, and psychological/behavioral) through innovative methods and collaborative efforts will ultimately yield the comprehensive understanding needed to fully capitalize on the potential therapeutic properties of these compounds.

Introduction

"Psychedelic" is a term first coined by psychiatrist Humphry Osmond in the 1950s, meaning mind manifesting [1]. The term psychedelic has been applied to several compounds that cause profound alterations in consciousness, including the perceptions of self, time, space, sensory impressions, emotions, and cognition. Although there is no agreed-upon definition, here we will focus on "classical psychedelics," sometimes described as "serotonergic psychedelics," which include psilocybin, lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), and mescaline, among others. All are agonists at various serotonin (5-HT) receptors, with the primary site of action for induction of the psychedelic experience being the 5-HT$_{2A}$ receptor [2,3]. Several of these compounds are naturally occurring and are produced by certain plant, animal, and fungi species [4–7].

The past two decades have seen a resurgence of interest in, and research with, psychedelics, beginning with initial studies in obsessive-compulsive disorder (OCD) and anxiety and depression associated with cancer [8,9]. Several recent studies have shown benefits of varying magnitude in treating depression, anxiety/depression associated with life-threatening illness, substance use disorders, and eating disorders [10–17]. These all have generally followed a model typically referred to as "psychedelic-assisted psychotherapy" (PAP), where 1–2 dosing sessions are preceded by psychological preparation and followed by psychological integration. These studies have shown both short-term persisting effects, i.e. hours to days after perceptual effects have subsided, and long-term persisting effects, i.e. those lasting weeks to months.

It remains unclear, however, how the administration of psychedelic compounds with therapeutic support from well-trained practitioners impacts the brain to promote therapeutic effects across a range of conditions with varying symptomatology. In this perspective, we summarize what is known about how these compounds work at a molecular, cellular, and brain network level, and we discuss how these changes may relate to potential therapeutic effects observed in severe psychiatric disorders. We conclude by highlighting a major ongoing controversy in the field, how it is informed by theoretical models from disparate levels of inquiry and discuss how future efforts to bridge these levels may lead to the most fruitful discoveries.

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Cellular/Neural Mechanisms

Receptor/Cell signaling

Classical psychedelics are small lipophilic molecules that readily cross the blood-brain barrier and distribute in the central nervous system [18]. These drugs share a common pharmacophore that allows them to bind and activate 5-HT_{2A} receptors [19], which are thought to mediate their subjective effects. The 5-HT_{2A} receptor is densely distributed in the cortex (particularly on layer V pyramidal neurons) [20] but is also expressed on inhibitory interneurons in the striatum, hippocampus, and amygdala [21–23]. It has been shown that occupancy at these sites correlates with the subjective intensity of the psychedelic effect [24]. Ketanserin, primarily a 5-HT_{2A} receptor antagonist with additional antagonist effects at 5-$HT_{2B/2C}$ receptors, can block these subjective effects in a dose-dependent manner [25,26]. The head twitch response (HTR) in rodents, thought to be an indicator of subjective psychedelic effects in humans, is also dependent on 5-HT_{2A} receptor binding and can be selectively blocked pharmacologically or genetically [27,28].

The 5-HT_{2A} receptor is a metabotropic serotonin receptor. When a psychedelic compound binds to this receptor, it activates G_q-like G proteins. This activation leads to a second messenger cascade that includes the hydrolysis of phosphatidylinositol-4,5-bisphosphate, leading to intracellular Ca^{2+} release by inositol trisphosphate and the activation of protein kinase C by diacylglycerol [18]. G_q-biased downstream signaling cascades appear to underlie differences in subjective effects between psychedelic vs. non-psychedelic 5-HT_{2A} agonists (e.g., lisuride, ergotamine). Specifically, preferential G_q protein signaling recruitment downstream of 5-HT_{2A} receptor activation was recently demonstrated to mediate the HTR in rodents, an effect that was dissociable from 5-HT_{2A} β-arrestin 2-induced tachyphylaxis and receptor down-regulation [29]. However, the comparability of 5-HT_{2A} G_q recruitment by classical psychedelics in humans and animals remains to be elucidated, as does comparability of psychedelic-induced β-arrestin 2 translocation and effects on tachyphylaxis/receptor down-regulation. Additional signaling pathways, e.g., arachidonic acid release, may be involved as well [19,30–32]. Classical psychedelics also bind with varying affinities to several other 5-HT receptors, including 5-HT_{1A}, 5-HT_{2B}, and 5-HT_{2C}, and they have varying agonist activity at dopamine and alpha-adrenergic receptors [33,34]. There is some emerging data in animals [35] and humans [36] to suggest that the therapeutic properties of psilocybin, specifically, may not be entirely mediated through the 5-HT_{2A} receptor and the subjective psychedelic experience, but more definitive evidence is needed to draw firm conclusions.

In addition to actions in the central nervous system, classical psychedelics have potent peripheral anti-inflammatory effects, likely through peripheral 5-HT_{2A} receptors [34,37]. Early studies utilizing rat aortic smooth muscle cells stimulated with TNF-a found that the psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI) could block the expression of several proinflammatory cytokines and adhesion protein genes in picomolar concentrations [38]. Experiments utilizing selective antagonists and 5-HT_{2A} receptor knock-out mice show that this effect depends on the 5-HT_{2A} receptor. Anti-inflammatory effects have been replicated in *in vivo* disease models, including cardiovascular and metabolic disease and asthma [39]. Intriguingly, effects are observed at doses that do not produce the HTR and that would not be expected to induce a psychedelic experience in humans. The relevance of the anti-inflammatory effects to the therapeutic effects of classical psychedelics is currently unknown.

Cellular changes

Classical psychedelics enhance neuronal excitability, primarily through activation of the 5-HT_{2A} receptor. When activated, this receptor promotes membrane depolarization, elicits a diminished post-hyperpolarization response, and reduces spike frequency adaptation [40]. Administration of psychedelics leads to a marked increase in glutamate release, activation of AMPA receptors, subsequent secretion of brain-derived neurotrophic factor (BDNF), and an increase in the expression of immediate early genes (IEGs) vital for neuronal plasticity, notably Fos, Arc, and Egr2 in the neocortex [41]. Beyond activating these IEGs, psychedelics may directly bind to the tropomyosin receptor kinase B (TrkB) as a positive allosteric modulator, prompting the enhanced signaling efficacy of neurotrophic factors such as BDNF, which results in mTOR activation and further production of plasticity-related proteins [42].

After psychedelic exposure, there are observable changes in structural markers of neural plasticity, encompassing enhanced synaptogenesis and dendritic growth, with less robust evidence for neurogenesis in the dentate gyrus of the hippocampus [43–45]. Investigations employing primarily neuronal cultures have shown that psychedelics alter spine size, increase spine density, and promote dendrite proliferation. These structural changes are not confined to in vitro settings; they have been observed in ex vivo tissue samples and in the intact brain *in vivo* [46–48]. Notably, modifications in spine density have been detected up to one month after a single administration of psilocybin in mice [47]. Emerging evidence suggests that both intracellular 5-HT_{2A} receptors and TrkB receptor positive allosteric modulation may be central to the neuroplastic effects of psychedelics [42,49]. This raises important questions about whether 5-HT_{2A} cell membrane receptor signaling, which appears critical for mediating the subjective effects of psychedelic compounds, is the endogenous target responsible for the well-documented neuroplastic effects.

3,4-methylenedioxymethamphetamine (MDMA) is a phenethylamine with stimulant properties that, in contrast to classical psychedelics, promotes fewer/less intense alterations in perceptual functions and is classified as an empathogen/entactogen because it primarily produces elevated mood, well-being, and prosocial behavior. MDMA promotes release and blocks reuptake of endogenous neurotransmitters (serotonin, norepinephrine, and dopamine, in descending order of elevation of extracellular neurotransmitter levels), which is the mechanism thought to underlie many of its subjective effects in humans [50]. Although the *R*-enantiomer of MDMA weakly activates the 5-HT_{2A} receptor and co-administration of ketanserin attenuates several subjective and physiological effects of MDMA, many subjective effects remain, including mood improvement, well-being, and extraversion [51]. In contrast, these effects are greatly attenuated when administered alongside the selective serotonin reuptake inhibitor citalopram [52]. These data converge with molecular evidence to suggest that the mood-enhancing and prosocial effects of MDMA are reliant upon presynaptic serotonin release via the serotonin transporter [53]. Despite differences in molecular mechanisms of action for inducing subjective effects, recent animal studies have drawn parallels between the neurobiological effects of classical psychedelics and those previously attributed to MDMA, which can similarly re-open a critical period of social learning in mice [54,55]. Specifically, adolescent mice will frequent spaces in which they previously had social contact, but this type of social conditioning declines in adulthood (i.e., the critical period closes). However, 48 h following the administration of MDMA, psilocybin, LSD, or non-5-HT_{2A} hallucinogens (i.e., ketamine and ibogaine), there is an adaptation in the nucleus accumbens, an oxytocin-mediated long-term depression in medium spiny neurons reflected in reduced frequency of miniature excitatory post-synaptic currents, that allows social contact to promote conditioning once more. The duration of this re-opening period was found to track closely the duration of subjective experiences elicited by psychedelics in humans; for example, ketamine, which can induce a subjective effect in humans anywhere from 1 to 6 h depending on the route of administration, induces a shorter duration period of critical period re-opening, whereas ibogaine, which can last from 12 to 36 h, was shown to exert a re-opening of this period for over four weeks. The duration of the critical period re-opening was similar between MDMA and psilocybin (~2 weeks), with both shorter than that of LSD (~3 weeks). The re-opening of the social

reward learning critical period induced by classic psychedelics was blocked by ketanserin, which did not block the re-opening induced by MDMA or ketamine, indicating that 5-HT_{2A}R agonism is required for this effect with classical psychedelics but is not necessary for all compounds capable of inducing critical period re-opening. However, both MDMA and LSD were unable to re-open the critical period in β-arrestin 2 knock-out mice, which suggests a possible common necessary downstream signaling pathway despite MDMA non-reliance on the 5-HT_{2A} receptor. Ketamine and ibogaine, another non-classical psychedelic, both demonstrated critical period re-opening in β-arrestin 2 knock-out mice, suggesting the necessity of this pathway for some but not all drugs capable of critical period re-opening. This re-opening of critical periods has been hypothesized to represent a type of "metaplasticity," believed to be mediated via extra-cellular matrix (ECM) remodeling, as evidenced by the enrichment of DNA transcription associated with the regulation of ECM [54]. However, the applicability of this animal model to humans and the translatability of critical period re-opening to the putative long-term neural changes induced by psychedelics in humans remains to be established. Interestingly, in vitro studies have demonstrated that MDMA and classical psychedelics both increase dendritic arbor complexity, and the effects of both classical psychedelics and MDMA on structural plasticity markers are blocked by ketanserin administration [43]. This discrepancy (ketanserin blocking structural plasticity promotion of both MDMA and classical psychedelics but permitting MDMA-related social reward learning critical period re-opening) implicates an interesting divergence in the pathways for MDMA-induced structural plasticity promotion (possibly dependent on 5-HT_{2A} receptor activation) vs. MDMA-induced social reward learning critical period re-opening (not dependent on the 5-HT_{2A} receptor but seemingly dependent on β-arrestin 2 signaling).

Circuit Level Effects

Neuroimaging studies have found inconsistent acute psychedelic effects on brain activity and connectivity, perhaps an artifact of predominantly small-sample resting-state studies in which variability in unconstrained cognitive operations differentially influences outcomes across studies. Utilizing fluorodeoxyglucose (FDG)-positron emission tomography (PET), a metabolic marker of brain activity, psilocybin acutely increased brain activity in the frontal and temporal lobes and decreased brain activity in the thalamus [56,57]. Likewise, functional magnetic resonance imaging (fMRI) studies utilizing blood oxygenation level dependent (BOLD) signal and measuring cerebral perfusion with arterial spin labeling (ASL) have found only decreases, only increases, or both increases and decreases under acute psychedelics [58–60]. Regarding resting state functional connectivity during acute drug effects, several studies have found decreased connectivity within canonical large-scale brain networks, such as the default mode network (DMN), salience network, and sensory networks. Increased connectivity has also been observed between brain networks, though the nature and magnitude of increases varies greatly across studies [61]. Increased connectivity has also been observed between much of the cortex and the thalamus [25,62–64], supporting a popular thalamocortical gating model of psychedelic action [65].

How these circuit-level changes manifested during acute drug effects in healthy individuals are associated with long-term changes in healthy individuals and favorable therapeutic response in patient populations has not been well characterized. One study examining long-term effects of psilocybin in healthy individuals found that, at 1 month after dosing, the number of positive resting-state fMRI functional connections across the brain (mostly within-network connections) increased from baseline, a time point during which they also found increased positive affect and decreased trait anxiety. Effects on emotion processing brain function in this study were more pronounced at one week but relatively indistinguishable from baseline at 1 month [66]. Additional work has examined post-acute changes in patients with depression. Two studies found that flexibility of brain function increased days to weeks following psilocybin therapy in patients with depression. One study found that persisting decreases in modularity (i.e., the tendency of the brain to group into networks) was associated with the magnitude of antidepressant response [67], and another study found persisting increases in the variability of functional connectivity, a measure of neural flexibility, was related to changes in cognitive flexibility [68].

The Raging Debate over Biology vs. Experience

The current set of findings conveys an impressive array of acute and post-acute neurobiological changes induced by psychedelic compounds across various levels of analysis, ranging from receptor-mediated downstream transcriptional changes to long-term neuronal structural alterations and functional changes in large-scale networks. However, this field remains in its infancy, and there are many unanswered questions and controversies surrounding psychedelics and psychedelic therapy. We discuss, below, one of the current most hotly contested areas and describe how it may be informed by perspectives originating from very different levels of scientific inquiry.

Is the "psychedelic experience" necessary for therapeutic effects?

It is currently widely debated whether the subjective experience induced by a psychedelic is necessary for promotion of enduring positive therapeutic effects. As described above, psychedelics have been considered "psychoplastogens," i.e. compounds that induce long-lasting up-regulation in plasticity of neural structure and function [43]. Many psychiatric disorders have been hypothesized to be associated with loss of neuronal structural components of plasticity, particularly in the prefrontal cortex, and reversing this loss has been postulated to be a component of effective therapeutics, as has been seen with SSRIs (after long-term use), ketamine, and psychedelics [69]. Recently, multiple psychoplastogens have been developed that, when tested in rodents, do not induce a HTR, which, as noted above, is a marker for the subjective psychedelic effects in humans. However, these compounds do produce robust changes in markers of neuroplasticity and demonstrate evidence of possible therapeutic effects in rodent models [41,70,71]. Thus, the subjective psychedelic experience may be dissociable from the neuroplasticity-promoting effects, and it remains unclear in humans which component, or both, are most critical for long-term therapeutic outcomes. A counterargument is encapsulated by the behavioral catalyst model, which postulates that the psychedelic experience and psychological insights gained are central to producing long-term changes in behavior and relief of symptoms [72]. In this model, the drug facilitates a transformative experience and enhances certain cognitive processes such as cognitive flexibility sub-acutely, allowing for greater benefit from subsequent psychotherapeutic interventions. In several trials, measures of the mystical experience correlate well with the therapeutic outcome, even after controlling for the intensity of the subjective psychedelic experience [16,17,73–77]. This would tend to support the behavioral catalyst model. In this model, the underlying biological mechanisms are necessary but not sufficient for the full therapeutic potential of these compounds to be realized. It may be possible to test this hypothesis by administering psychedelics under general anesthetics, as has been done with ketamine, or compounds that block the formation of episodic memories, such as midazolam or scopolamine, thus removing the subjective experience or memory of the subjective experience [78]. However, this approach also induces major confounds related to the anesthesia/memory-blocking drug itself, which may exert its own distinct effects on relevant circuitry [79]. Another approach would be the administration of psychedelics with other medications that block the subjective effects, such as ketanserin or risperidone [80], which would eliminate the subjective experience through 5-HT_{2A} antagonism but may also exert unintended detrimental effects on subsequent promotion of neuroplasticity given that 5-HT_{2A} receptor binding may or may not also

mediate this property [18,35,42,49]. To our knowledge, there are no psychedelic compounds that lack psychoplastogenic properties, but such compounds would be an extremely useful tool in resolving this controversy. Additionally, there may be non-pharmacological methods of inducing psychedelic-like states that may lack psychoplastogenic properties, e.g., altered breathing patterns, visual stimulation, sensory deprivation, and virtual reality, but it is currently unclear how such methods may or may not replicate key neurobiological changes that characterize the psychedelic experience [81–83].

"Microdosing," which involves the administration of sub-perceptual doses of psychedelics, typically 1/10th of a recreational dose, usually every other or every third day for several weeks to months, could also shed light on this controversy [84,85]. The current evidence base for the beneficial effects of this approach is largely unsupportive, and expectancy effects may play a large role in uncontrolled studies [85,86]. However, the manifestation of psychoplastogenic properties is both substance- and dose-dependent. A presumably sub-perceptual dose of DMT, 1 mg/kg, increased functional plasticity in rat cortical slices [43], whereas a perceptual dose of 4 mg/kg of psilocybin was required to induce neuroplasticity-related changes in gene expression in rat PFC [87]. Thus, it may be the case that protocols could be developed utilizing more "potent" psychoplastogens at sub-perceptual doses that might inform on the importance of plasticity vs. subjective experience on therapeutic outcomes.

This debate directly ties into the related question of the role of psychological support or psychotherapy in treatment response and what amount/type is optimal. Currently, there is no standardization on type or amount provided in clinical trials, and what is documented in trials is extremely heterogeneous [88]. However, the psychological component generally consists of preparation, a non-directive, supportive approach with minimal interaction during dosing, and one or more sessions of integration, which is also non-directive. If the psychoplastogenic effect is primarily responsible for the therapeutic effect, only a minimal amount of safety-focused psychotherapy or psychological support would theoretically be needed. For example, a recent small study utilizing DMT with minimal psychological support showed a substantial antidepressant effect [89]. If the behavioral catalyst model of psychedelic therapy is accurate, the psychological component could be expected to substantially contribute to the therapeutic effect. Therefore, the provision of evidence-based psychotherapy would be expected to further enhance therapeutic outcomes, e.g., cognitive behavioral therapy (CBT) and/or motivational enhancement therapy (MET) [88]. Finally, if psychedelics do open a window of plasticity that is enhanced and/or shaped by the psychotherapy component, it is possible that other post-psychedelic interventional modalities would prolong or enhance these benefits. Neuromodulation would be one such promising modality to examine, as certain forms are already FDA-cleared for treatment and act directly on the brain to remediate circuitry [90,91]. Clearly, an effective arbitration of these competing hypotheses (or a unification of them) would greatly inform scientific understanding and may also translate to improved treatments.

Bridging the chasm in levels of inquiry: a potential solution?

We argue that a comprehensive and pragmatic understanding of how psychedelics impact the brain and body to promote therapeutic benefit requires bridging multiple levels of inquiry (molecular, cellular, neural circuit, and psychological/behavioral; Fig. 1) that currently characterize disparate and largely non-interacting levels of research. There are several prevailing theories and models that tend to emphasize a particular unit of analysis, i.e., the psychoplastogen model on the cellular level, the thalamocortical model on the neural circuit level, and the behavioral-catalyst model on the psychological/behavioral level [65,92]. It may one day be possible to resolve these models under a common grand unifying principle, but currently, our understanding of psychedelic mechanisms across these levels remains concurrent, independent, and separable. Identifying testable hypotheses and designing experiments that bridge levels of analysis will be necessary to answer unresolved questions. This ultimately requires an enhanced array of scientific tools that would facilitate a connection between, for example, macro-level circuit changes during or after psychedelic administration with non-invasively derived markers of synaptic plasticity, changes in protein expression or gene transcription, and characterization of acute and long-term psychological and behavioral changes. Invasive studies in animal models are better poised to initially cross this divide through comprehensive imaging, transcriptomic, and behavioral assays, but the inherent challenge of translating laboratory animal models to accurate insights in humans remains a major limitation. Human studies could also better bridge the circuit to psychological/behavioral level through use of task-based rather than resting-state neuroimaging. However, with the increased interest and funding in this exciting area, we are hopeful that multidisciplinary collaborations amongst the brightest scientific minds

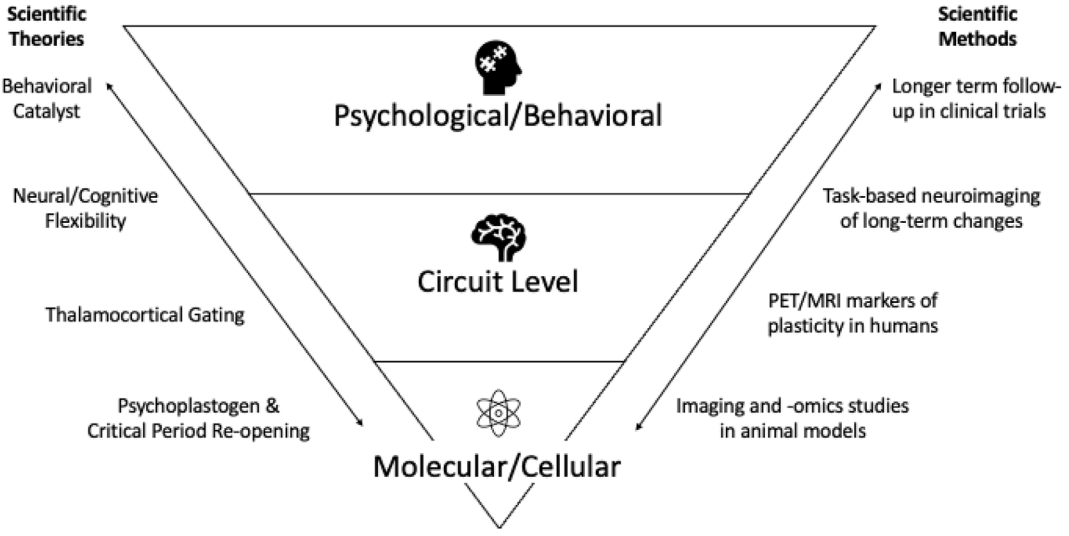

Fig. 1. Levels of inquiry in research of classical psychedelics. The current levels of scientific inquiry into the actions of classical psychedelics include the level of molecules and cells, neural circuits, and psychological and behavioral. Displayed on the left side of the figure are the current theories alongside the relative level of inquiry that they attempt to explain. On the right side of the figure are suggested research methods to help bridge these levels of inquiry and develop more unified models.

will build the proverbial bridge so desperately needed to generate insights across levels and species. Ultimately, how psychedelics, across varying levels of neuroscientific inquiry, promote the potentially robust and long-lasting therapeutic changes observed in recent large-scale studies remains an exciting and unanswered question that will generate spirited debate and controversy for years to come. However, the "quantum leap" in our understanding of these powerful and potentially very useful therapeutic tools will be forged in the crucible of confusion that currently characterizes modern understanding.

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Author Contributions

Dr. Fonzo and Dr. Barksdale conceptualized the manuscript. Dr. Barksdale drafted the initial manuscript. Drs. Fonzo, Doss, and Nemeroff provided critical feedback and revised the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

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