MIND FOUNDATION

Leave the trips alone

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> *The question of whether the "psychedelic trip" is truly needed for the therapeutic benefits of psychedelics has become a matter of heated debate. This fact is best illustrated by two recent opposing publications: one by David B. Yaden, PhD, and Prof. Roland Griffiths,1 advocating for the importance of psychedelic experience, and one from Dr. David Olson,2 who claims we could (and perhaps should) discard it. This post gives a neuroscience-based argument for why we should not ignore the human experience.*

A recent paper from Dr. David Olson's lab at University of California, Davis, made waves in the psychedelic research community at the end of 2020, describing a non-hallucinogenic derivative of the psychedelic drug ibogaine, named Tabernanthalog (TBG).3 Ibogaine is known to have antidepressant and antiaddictive properties, but it is restricted in its use by an unfavorable safety profile that includes nausea, cardiac complications,4 and a duration that can exceed 24 hours.5 TBG, on the other hand, is shown to maintain ibogaine's therapeutic effects in mice without the associated risks. Most importantly, this compound made it to the headlines of several science magazines because mouse experiments suggest that it lacks hallucinogenic properties. Although being allegedly trip-free, TBG is shown to enhance neuroplasticity in the mouse cortex, just like its psychoactive counterpart ibogaine. Comparing the effects of ibogaine with those of TBG may allow scientists to answer a heated question in psychedelic research: can therapeutic benefits occur without the subjective effects? If classical psychedelics increase neuroplasticity and decrease inflammation to an antidepressant effect, is the trip even necessary?

THE NEUROBIOLOGY OF TRIP-FREE PSYCHEDELICS

Psychoplastogens [Greek psych– (mind), –plast (molded), and –gen (producing)]: small molecules that produce a measurable change in neuroplasticity (e.g., changes in neurite growth, dendritic spine density, synapse number, intrinsic excitability, etc.) within a short period of time (typically 24-72 hours) following a single administration, and that can lead to relatively long-lasting changes in behavior.6

Even though nearly all identified psychoplastogens (e.g., psilocybin, DMT, ketamine, scopolamine) are psychoactive, this characteristic is not part of their definition. The reason for this is that some scientists now believe that neuroplasticity can be rapidly stimulated even in the absence of a subjective experience, leading to an antidepressant effect.

One particularly effective pathway for stimulating neuroplasticity involves the serotonin 2A receptor (5-HT2AR),7 which is also necessary for the hallucinogenic effects of psychedelics.8,9 For several decades, drugs that stimulated the 5-HT2AR were considered to have a high risk for producing hallucinations, which severely discouraged their development. However, recent theoretical advancements in pharmacology indicate that neuroplasticity and the psychedelic experience may not be a package deal after all.10 To understand that, we need to zoom into the neuron itself and understand a process called biased agonism.

Figure 1: Potential therapeutic mechanisms of (non-hallucinogenic) psychedelics at the cellular level. *On the left side, the antidepressant effect of classical psychedelics is achieved through both the psychoplastogenic and subjective effects, using different signaling pathways; on the right, the antidepressant effect of a non-hallucinogenic psychoplastogen is only achieved through an increase in neuroplasticity; the latter compound is a biased agonist – it preferentially activates the Gq/PLC pathway, bypassing – or at least greatly reducing – the subjective effects.*

When a drug binds to a receptor on a cell, a number of biochemical chain reactions (also called signaling pathways) are triggered inside the neuron.11 Each of these reactions has a different end-point; this could be the production of a new protein or a change in electrical activity, which further lead to complex changes such as modifying the communication between different brain areas and producing new connections between neurons. When a biased agonist binds a receptor, it preferentially activates one or several of these reactions to the detriment of the others.10

In the case of the 5-HT2A receptor, there are three important signaling pathways inside the neuron: the Gq/PLC, the PLA2, and the beta-arrestin pathways.10, 12 While the details are not entirely clear, all of the cognitive and neurobiological effects that are attributed to 5-HT2AR activation (from visual hallucinations to neuroplasticity) can be traced back to one or several of these signaling pathways. A biased agonist could activate, say, the Gq/PLC pathway, without affecting the other two. In an ideal scenario, the psychoplastogenic effects sit at the end of one pathway, while the hallucinogenic effects are at another. Some evidence suggests that this might actually be the case: a recent paper concludes that beta-arrestin 2 is required for the “psychedelic-like” motor effects seen in mice (i.e. head twitches, retrograde walking, nose poking).13 As a complement, it was previously shown that neuroplasticity is associated to the Gq/PLC pathway,14, 15 which also appears to have a reduced influence on “psychedelic-like” motor effects in mice.16 Lastly, the Gq/PLC pathway is also activated by lisuride, a non-hallucinogenic relative of LSD, further suggesting that the subjective effects lay elsewhere.17

Tabernanthalog: Breakthrough Treatment, Patented Microdose, or Neither?

There is some consensus that a positive psychedelic experience can bring larger therapeutic benefits, as revealed in a spirited debate between Yaden and Olson, the two researchers who gave structure to this line of research. Nevertheless, scientists in the psychedelic industry are trying to engineer a compound that retains some of the therapeutic potential but is also scalable, marketable, and administrable to people who do not pass the screening process for a psychedelic experience. TBG seems to be a strong candidate for a widely administrable non-hallucinogenic psychoplastogen. But does it really live up to its hype?

Let us analyze this compound a bit more in depth, starting with its most outstanding feature: lack of hallucinogenic properties. Most animal studies on the hallucinogenic potential of psychedelics are based on the mouse head-twitch response. This is considered the gold-standard for assessing psychoactive effects of classical psychedelics in mice, as several studies have shown a correlation between how well a drug binds to the 5-HT2AR, the intensity of the hallucinations in humans, and the head-twitch response.18, 19, 20 However, apart from the obvious problem that a head motion is a far cry from a window into the subjective experience of a mouse (what is it even like to be a mouse?), there are some important limitations that are worth mentioning.

In the TBG paper, it is shown that a high dose of ibogaine also does not produce a statistically significant increase in head twitches, which is in line with a previous study.21 Yet ibogaine is undeniably hallucinogenic in humans.4 Moreover, the serotonin precursor 5-HTP produces a robust head twitch response in mice,22, 23 while being psychologically inert in humans. This means that until a human being ingests TBG, there can be no definitive claims regarding the hallucinogenic properties of this compound, nor can one yet postulate the existence of atherapeutically viable non-hallucinogenic psychoplastogen. TBG is not the first attempt in this direction, as other proposed psychoplastogens closely related to ketamine have either been proven psychoactive (traxoprodil), or ineffective in treating human depression (AZD6765, rapastinel).24

For now, we shall assume that this compound is indeed non-hallucinogenic in humans. On a close reading of the TBG paper,3 it is revealed that the maximal activation of the Gq/PLC pathway (i.e. the pathway more associated with neuroplasticity, rather than hallucinations) of the 5-HT2A receptor by TBG is almost half of that of ibogaine, 5-MeO-DMT (another potent hallucinogen), and serotonin itself. Remembering the hypothetical example given in the section above, an ideal non-hallucinogenic psychedelic would minimally activate the intracellular pathway that leads to a psychedelic trip, while strongly stimulating neuroplasticity. But TBG may or may not have any preference for one pathway or another at the 5-HT2AR, and due to its intrinsic properties, it may simply not be able to activate any of these pathways to the same extent as its hallucinogenic counterpart ibogaine. What this would really mean is that a large dose of TBG weakly stimulates 5-HT2ARs in a way that is similar to a microdose of DMT, which has also been shown to produce some antidepressant and anxiolytic effects in mice.25

TBG could be a billion-dollar molecule – it is patented, it may treat both depression and addiction, it is synthetized in one step, and it may not make people trip, even if they take more of it (A more in-depth critical look into the commercial incentives for such compounds can be found in this article on the APRA Blog). From a pharmacological point of view, however, TBG doesn't seem much different from already existing solutions. And even though the authors of the TBG paper emphasize a shift in the perspective on mental health care from correcting "chemical imbalances" to correcting "damaged circuits,"6 there is still not a single mention of the human experience, making it seem like this is not the kind of paradigm shift some practitioners are calling for.26

Neuroplasticity and Experience

Now that we explored the neurobiology of non-hallucinogenic psychoplastogens, let us get to the key point of neuroplasticity itself. Neuroplasticity has become a buzz word in psychedelic research recently, wherein many are reducing the therapeutic benefits of both novel (e.g. ketamine, psilocybin) and classical antidepressants (selective serotonin reuptake inhibitors such as fluoxetine) to it.27 But can an increase in plasticity alone do the job of changing one's mind?

Firstly, what even is plasticity? Put broadly, it's the brain's ability to change its structure and functions through brain activity. More concretely, neuroplasticity is an umbrella term that encompasses several dynamic processes that modify how neurons communicate with each other.28 In a hardware-software analogy of the brain and mind, neuroplasticity would represent the processes through which the software (brain activity) modifies the hardware (neuronal circuits).29 These processes include modifying the strengths of existing connections, creating new connections (via newly grown neuronal branches called dendrites), and eliminating old ones.

Some believe that people develop depression through a pathological loss of connections, most notably in the prefrontal cortex,27, 7 and that psychoplastogens can repair or rebalance these circuits.6 What is rarely emphasized in this particular discourse is the fact that the brain is a profoundly organized, hierarchical organ. This means that each connection has a precise function and significance, and plasticity (just like brain activity itself) is not a haphazard process, but a carefully orchestrated cascade in which useful connections become enhanced and obsolete or redundant ones atrophy. Importantly, the usefulness of these connections is assessed locally, through principles of homeostasis and harmonious activity, and may only weakly correlate with good mood, happiness, or fulfillment. Evolution has likely optimized our nervous systems for functioning and survival rather than psychological flourishing. It is therefore unlikely that the brain will attune to these positive feelings by itself, through sheer cellular processes that are induced in an unspecific manner.

So, what exactly would those psychoplastogens restore? The elimination of connections is as crucial to brain development and functioning as the creation of new ones, meaning that more connections are not necessarily beneficial by themselves. Dr. David Olson, head of the team who coined the term psychoplastogen and discovered TBG, stated that "the most useful psychoplastogens will be the ones capable of promoting plasticity in a circuit-specific manner. […] Promoting plasticity indiscriminately is not likely to be beneficial."6 Ergo, what truly matters is which connections are formed or lost, and the persistence of that change over time. Even in the seminal paperwritten by Ly et al.7 (summarized in this MIND blog post), which turbocharged the whole discussion about neuroplasticity and psychedelics, it is unclear how long the new connections between neurons persist, let alone what they mean.

Generally, plasticity happens as a direct consequence of coherent neuronal activity, as exemplified by the famous quote from neuropsychologist Donald Hebb: "Neurons that fire together, wire together". Psychedelics and ketamine seem to enhance this process by opening a window of opportunity for plasticity, which is closely preceded by a flow of thoughts, emotions and imagery, some which follow a subjectively deeply meaningful narrative thread.37

In relation to a psychedelic trip, it has been shown that interpersonal exchanges, mystical experiences, and personal insights correlate with the persistence of the therapeutic effects in patients who had them.1, 30, 31, 32 What is interesting is that the presence and strength of a mystical-type experience — and not the *overall* intensity of the experience — correlated with the therapeutic benefits.1

The effectiveness of MDMA in treating PTSD is also highly dependent not only on setting, but also on the experiences that follow the acute dose. This appears to hold true as long as that window of neuroplasticity remains open – spanning at least two weeks, according to one study.38 As Dr. Gül Dölen, MD, PhD, Associate Professor at Johns Hopkins University and MIND Foundation Scientific Advisory Board member, said in an interview for the MIND Blog: "Any drug or any manipulation that can reopen the critical period has the potential for that therapeutic effect. But then on top of that, the setting dependence of it means that what the psychedelic journey is doing and the setting is doing is priming the brain so that the right memory and the right circuit is being brought into reactivation or made available for modification in this open state." It is beyond doubt that all experiences have aneurological correlate, a trace or an "engram," but due to the complexity of brain architecture, there is no technology that can identify and change circuits that are linked to a specific traumatic memory, or to a detrimental behavior. It seems like the only window we have into these circuits is through the act of remembering.

In other words, particular altered states of consciousness (like those induced by psychedelics, but potentially extending beyond them), which are triggered by (or at least generally oriented towards) the therapeutic problem, would be the curators of the beneficial and specific kind of plasticity that is likely to last and be reinforced. However, without that experience, psychoplastogens could just cause a transient increase in indiscriminate cortical connections.

Rooting for the Human Experience

The point of this article is not to belittle the efforts of the many scientists searching for non-hallucinogenic psychoplastogens, but to give some depth to the argument favoring the importance of the psychedelic experience, from a neurobiological point of view. Why is this important? Neuroscientific discourse has become central in any discussion about mental health, even in situations in which we don't know exactly what psychological processes we're dealing with. There is a tendency in psychiatry to delineate illnesses with fuzzy borders and equate them to neurobiological markers which are subject to repair. This tendency, fueled by a pharmaceutical system in which drug development, prescriptions, and shareholder value are inextricably linked, leads to the proliferation of simplistic and marketable solutions to poorly understood problems.33

The advent of psychedelic therapy raises hopes for a reform of how we understand the brain, the mind, and its various deviations from the norm. In spite of exuberant enthusiasm from some parties, psychedelics are not a magic bullet for the mental health crisis. But their re-emergence has – if nothing else – given center stage to the human experience, not just as an outcome measure of symptom severity, but as a mediator of change.39 Reframing psychedelics as psychoplastogens, turning the discussion from "correcting chemical imbalances" to "correcting circuit imbalances," and framing the psychedelic experience as costly and unscalable misses that point entirely. Nobody doubts the transformative potential that the birth of one's child, a peak experience,40 or a close brush with death can have on one's life. Many people compare their psychedelic experiences to all of the above and even rate them as among the most meaningful experiences of their lives.34

It is true that those who undergo psychedelic therapy require special care and attention, but perhaps that's what it takes. Viewing care as a cost to be cut has already produced a system of 'managed care,'41 wherein people are prescribed antidepressants without seeing a therapist, leaving up to one third of patients inadequately treated.33,35 Patients who have undergone both types of treatments underline this sentiment: "[Antidepressants are] like taking a painkiller for a toothache, you don't get to the source of the problem".36 Many associate established antidepressant medications with an avoidance of the underlying cause of their depression, even exacerbating a feeling of disconnection, which contrasts with psychedelic therapy.36

For those who cannot pass the screening required for psychedelic therapy, non-hallucinogenic psychoplastogens could represent another chance, if they turn out to exist and work. If not, microdosing could also be an alternative, if proven effective as an antidepressant in the future. However, it clearly does not seem sustainable to simply keep prescribing pills and releasing a large number of patients back into the same environment in which they developed their depression in the first place.

There is a risk that the market could take trip-free psychedelics as a coarse but sufficient distillation of classical psychedelics, and choose not to deal with the trip due to the numerous complexities in its implementation in mental health care. What appears now to be the way to a mental health revolution could fizzle out into a skillful rebranding of failed treatments, at the expense of people who cannot recover a sense of meaning and connection to this world and to other people. If psychedelics would become psychoplastogens in therapy, psychiatry may once again close its doors to human subjectivity just as it is tip-toeing back to its rightful place.

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