LSD and Perception: the Bergson-Gibson Model for Direct Perception and its Biochemical Framework

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(*Psychology of Consciousness*, In press)

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An early portion of this research was coincident but unrelated to a research assistantship to David R. Logan, supported by Ann L. Kelsall and the Farnesol and Candida Albicans Research

Fund, University of Nebraska Foundation, to Professor Kenneth W. Nickerson. The authors have no known conflict of interest to disclose.

The authors are grateful to Kai Johnson, University of Nebraska-Lincoln, for useful discussion, to Professor James Manning, Northeastern University, for a helpful clarification, and to Professor Ken Houk, University of California-Los Angeles, for a helpful comment on the work of Domelsmith, Munchausen, & Houk (1978). The authors are also grateful to the editor of Psychology of Consciousness and to two anonymous reviewers whose suggestions helped to clarify the manuscript.

A very preliminary portion of this research was disseminated on the YouTube channel of Stephen E. Robbins (Robbins, 2019).

The authors contributed equally to this work.

Abstract

A general assumption in LSD research is that LSD's experiential effects are basically hallucinatory, varying in the degree of distortion. This likely derives from the widely and perhaps implicitly held position of indirect realism which, though accepting an objective world, assumes the brain is generating within the mind not only imaginative images and memory images, but also perceptual images–with no substantive difference in their qualia. However, the origin of perceptual images permeated with qualia is an aspect of the "hard problem" of consciousness. And without a solution to the origin of images, any theory of LSD's seemingly distorted images of the perceptual world is ungrounded.

Currently, a model describing LSD's perceptual effects in terms of direct perception is created by joining Henri Bergson's panspychism and J. J. Gibson's ecological optics. In this model, different doses of LSD produce different timescale changes in perception, and these changes are veridical specifications of the external world, not hallucinatory. In this context, the brain is a very concrete dynamical device, one not captured by an abstract computational framework.

A testable model is proposed by which LSD increases rate processes on the relevant timescale. A variety of biochemical data are argued as being productively understood in the context of Gilbert Ling's association-induction hypothesis, and a primary sequence analysis of the "inductive index"–an amino acid score that is central to this hypothesis–is consistent with the importance of 5-hydroxytryptamine receptor 2A. The proposed model is compared to recent progress in structural biology.

Keywords: perception, LSD, Henri Bergson, J.J. Gibson, biochemistry

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Recently, several reports helped to clarify the neural, phenomenological, and biochemical changes underlying the effects of lysergic acid diethylamide (LSD). For example, cognitive neuroscientists revealed correlates to the LSD experience (Carhart-Harris et al., 2016; Preller et al., 2019) and helped to frame a theoretical basis for the psychotropic effects (Carhart-Harris et al., 2014; Preller et al., 2019; Atasoy et al., 2019). Theorists aligned with at least two prominent models of consciousness applied their work to these findings (Integrated Information Theory: Gallimore, 2015; Tononi et al., 2016; Predictive Processing: Hohwy, 2013; For review: Swanson, 2018). Also, structural biologists characterized features important for LSD signaling at the essential 5-HT_{2A} receptor (Wacker et al., 2017; Kim et al., 2020). But in this current research and theoretical effort, there is a major problem we wish to point out, and an alternative direction we wish to describe.

If there were a short phrase that describes the common theoretical stance towards the effect of psychedelics on brain function, it would be: "all is *hallucination*." The various perceptual effects that are said to characterize, for example, LSD–things like "time distortion," apparently enhanced visual acuity, pulsating objects, vibrant colors–are all taken to be in the same category as hallucinations in general, to include bugs crawling out of the wall, or other strange visual displays. In fact, not too much attention is paid in either the empirical studies or in the theoretical work as to whether the subject has their eyes open or closed–both states are considered nearly equivalent. This approach is anchored in the concept that the brain generates the image of the external world; in fact, it generates all images–internal images or imaginative images as well as the image of the coffee cup out there on the kitchen table. It is, in other words, an implicit acceptance of the theoretical perspective termed *indirect realism:* the world out there–the coffee

cup with the stirring spoon–is indeed objective, but the image thereof is generated by the brain and is somehow within the mind or mental sphere along with all other "internal" images. But the difficulty is that neuroscience has no model of how the brain and its neural mass creates or produces images–it is simply a faith that it does. How it does so is part of the "hard problem" (Chalmers, 1995), for the image of the external world is replete with qualia–the "whiteness" of coffee cup, the "clinking" of the spoon, the "brown" of the coffee–and since, in fact, there is nothing in our image of the external world that is *not* qualia, one can argue this is the more general statement of the problem: how to account for the origin of the image of the external world, whether via a computer architecture, a neural net, or a mass of neurons (Robbins, 2013).

But this problem is utterly unresolved. Therefore, it should at minimum cause some suspicion that the current effort on the operation of psychedelics is theoretically ungrounded. The suspicion could go further, for the indirect realism assumption could be misdirecting–at least partially–the research questions that should be asked.

In this paper we will describe a model of perception based in Bergson's (1896/1912) panpsychism, and integrated with J. J. Gibson's (1966, 1971) ecological optics. This joint framework is a model of *direct perception*, and a model of the origin of the image of the external world. It integrally incorporates *scales of time* in perception, ties these to (objective) action by the body and thus to the veridicality of perception, explicitly addresses the nature of the "information" being processed by the brain (always only vaguely described if at all in current theory), and elucidates the relation of the brain to memories that make sense of the "flood of information" into the brain featured in current psychedelic theory (Winkelman, 2017). Furthermore, it is the only theoretical framework that explicitly describes the origin of the image of the external world and the brain's role in this, essentially as an *optical* problem. No other theory does so; all others–to make a quick and broad characterization–rely upon an implicit or explicit

appeal to “emergence” (e.g., from complexity of networks/processes) or upon a panpsychic framework which, without being embedded in Bergson’s form of panpsychism as we shall discuss, is unable to address the problem of the origin of the image of the external world.

We shall focus only on LSD, for while there are structural similarities to substances like psilocybin and DMT, and likely similarities in causal action, there are also such major differences in effects that we risk a fatal mixture regarding clarity. For example, Strassman (2001) noted certain major categories of the DMT experience, and one of these, experienced consistently (and in a few seconds) by numerous subjects as though it were an objective reality with standard features, is a dimension of “aliens” with the subject being medically examined. This is simply not a dimension of LSD.

There are somewhat LSD-similar phenomena described in the literature on the “Alice in Wonderland” syndrome, but because there are perceptual distortions involved does not mean the same mechanism underlying LSD is at work. More crucially, these Alice-phenomena (e.g., a huge, outsized coffee cup) may indeed be pure hallucinations or perceptual distortions with no hint of veridicality.

Veridicality brings up an important aspect of this paper, namely, what will constitute *proof* for the theory presented? Two people, A and B, both ingest 75 mcg of LSD, and both see the same fly, at a new scale of time, hovering as a near-motionless being, its wings barely moving. Both are able to reach out slowly, at leisure, and grasp the fly by a wingtip. Given that the action indicated by the fly’s near-motionlessness was indeed realized, we would say this is a veridical perception, in turn a signal that A and B share an objective world. The indirect realist, however, can say that both A and B simply have–via some yet to be explained mechanism–“internal” brain-generated images (effectively hallucinations) of the fly at this new scale. In this indirect framework, the fact that action corresponds precisely to the specified state of the fly is a magical correspondence–a

"veridical hallucination" so to speak–with no in-principle hypothesis behind this match, it being only an ad hoc feature of the theory. Unconstrained due to being vague and in the grips of the hard problem, indirect realism can yet certainly make this assertion. This is inescapable. Judgement will then come down to evaluation of the structural consistency of the Bergson-Gibson framework that, a) describes a dynamical mechanism for specification of the image of the external world, b) integrally incorporates a specified scale of time for the image, and c) integrally ties the timescale to possible action, and logically necessitates the theoretical framework of this action-perception relation. Regarding LSD, we shall argue:

- Up to a certain dose, the LSD perceptual changes are veridical, for example increases in visual acuity, the slowing of ordinary objects (such as the blades of a fan or the wings of a fly), increased spacing between auditory events, and others.
- These perceptual changes are modifications of the scale of time at which the brain is specifying the external world.
- We believe there is a biochemical basis for this, which shall be described.
- As dose increases, the brain is increasingly opening to a flood from what Bergson termed "the virtual" (1896/1912), i.e., past experience.
- The timescale changes of the perceptual image are intrinsic implications of the Bergson-Gibson model.
- Scaling with dose, the "flood of information" (Winkelman, 2017) to brains on LSD must be construed within Bergson's model of memory, itself integral to the model of perception.

Current Frameworks for the LSD Experience

The Entropic Brain

In a landmark study, Carhart-Harris et al. (2016) investigated the effects of 75 mcg LSD on the human brain. Complementary neuroimaging methods revealed several brain regions were highly activated by LSD, well beyond resting state levels. Increased blood flow to the visual cortex and a "greatly expanded" functional connectivity profile of the primary visual cortex was observed, together with increased connectivity among brain regions associated with vision, attention, movement, and hearing (i.e., the perceptual-motor regions). Decreased connectivity was observed between the parahippocampus and retrosplenial cortex, regions associated with maintenance of the sense of self.

Carhart-Harris et al. (2014, 2016) proposed an "entropic" framework for the psychedelic state: LSD breaks down or disrupts the organization of the brain, the normal intercommunication among areas, increasing with dose, descending to greater disorder (greater entropy). A prime focus of this proposal was the default mode network (DMN) with its subsystem, the medial temporal lobe (MTL). If disrupted, our tie to reality is degraded. This concept was anchored within a Freudian context distinguishing "primary" and "secondary" consciousness, by which secondary consciousness is tied to reality, to the objective; it is maintained by the fine balance of certain major systems, e.g., the DMN/MTL–and these are part of that breakdown noted under LSD. In contrast, primary consciousness is unconstrained by reality; it is the consciousness of infants and seems to be very nearly, if not fully, hallucinatory.

For a theory dealing with a psychedelic that brings about large changes in perception, Carhart-Harris et al. curiously use the term "perception" but once (2014). The source of this de-emphasis is likely found in indirect realism–the "default mode" of current cognitive theory–and its assumption that conscious experiences, including conscious perception and our experiential image of the coffee cup on the table, are simply generated by the brain. In this framework, there is no difference between internal imagery or hallucinations, and perception. This de-emphasis on

perception (or its equivalence to dreams) is perhaps the cause of the subsequent de-emphasis of one of the main findings–the perceptual-motor regions lighting up, with "increased communications". This finding does not fit with disorganization or an increasing entropy in/of brain regions, and the authors opted to assess the increased blood flow to the visual cortex as unreliable, and argued these findings, essentially, are to be ignored.

The Thalamic-Gating Model

In another landmark study, Preller et al. (2019) investigated the effects of 100 mcg LSD on the thalamus filter system. The structure of interest was the cortical-striatal-thalamo-cortical (CSTC) feedback loop, and the nodes of interest were the posterior cingulate cortex (PCC), the ventral striatum (VS), the thalamus, and the temporal cortex. The latter is associated with memory and "processing emotional and social information" (Preller et al., 2019). LSD was proposed to create an abnormal flow of information into the cortex and to result in cognitive disruption, dreamlike experience, and ego dissolution.

Preller et al. noted the PCC is associated with arousal, awareness, and control of the balance between internally and externally directed thought (2019). Failure to suppress activity of the PCC is therefore associated with the intrusion of internal mentation or an "overload" (Preller et al., 2019). Importantly, the PCC is a core hub receiving information from other regions of the DMN, the medial prefrontal cortex and angular gyrus, for example.

Theories of Consciousness and LSD

At least two prominent theories of consciousness were applied to these findings. Integrated Information Theory (Gallimore, 2015; Tononi et al., 2016) is a network theory of consciousness and, by this, LSD was proposed to loosen causal constraints as the brain regresses toward entropy and chaotic experience (Gallimore, 2015; Swanson, 2018). However, Integrated Information Theory is not a theory of perception, and has limited resources to explain how the

relevant networks generate an image of the external world, relying implicitly on emergence from the complexity of interactions.

Predictive Processing relies upon predictive hypotheses or priors that are projected towards neural input from the external world (Hohwy, 2013). For example, the image of stirring coffee is projected toward the optic and sonic information arising from the event as it moves "upward" (Hohwy, 2013) along neural pathways. When there is a match between these upward inputs and a downward prior, the downward overrides the upward and one sees a predicted image. If there is not a match, adjustments to the perceived image are made to minimize predictive error (Hohwy, 2013). This viewpoint is theoretically possible, only because Predictive Processing holds that our percepts of external objects employ the same neural pathways as our mental images, our dreams, our hallucinations, and that the ability of the brain to generate an internal simulation or model is critical to our perceptual experiences. Predictive Processing offers multiple avenues of tie-in to LSD and the hallucinatory framework, but generally, the "core intuition" of Predictive Processing in this regard seems that "psychedelic drugs (somehow) interfere with established priors that normally constrain the brain's generative models" (Swanson, 2018, p. 16). Yet Predictive Processing is not a theory of perception. It has no actual theory of how the brain "generates" images–hallucinatory, imaginary or perceptual, or its priors for that matter, though its essence again, in regard to LSD, is that all is a form of hallucination.

Contraindicators: All is *Not* Hallucination

Our understanding of the alteration of perceptual experience under LSD relies obviously upon subjective reports. But it relies equally upon how these reports are interpreted, and worse, how they are routinely described. The standard mode of description for LSD experience is canted in favor of the hallucinatory framework and is reflective of the default philosophical base of an indirect realism. What we see, as general descriptors of the LSD effects, are:

- Impaired sense of time
- Distorted perception
- Euphoria
- Feelings of detachment
- Delusions
- Visual hallucinations

But “impaired sense of time” and “visual hallucinations” obscure the nature of that which is reported. For example, an LSD user commented:

> You see the same world, just differently. There are no unicorns or dragons. It's subtler than that. Rooms seem to shrink and swell gently, as if breathing. Your face changes subtly as you look at it in the mirror, facial hair appears to grow before your eyes, and clouds look like they fold in on themselves as they float across the sky. Visual acuity is increased; it is easier to notice and follow birds or insects as they fly, for example. Aural acuity too; you notice parts of songs that you never have before (and that are still there when listening sober). You don't actually see things that aren't there unless you take a very high dose. (Koben, 2014)

In other words, this LSD user experienced altered perception and not necessarily hallucination. While the degree and form of this effect would depend obviously on the dose, this view of altered perception is reinforced by the current trend in “microdosing” (Rifkin, Maraver, & Colzato, 2020). A microdose is less than 20 mcg, or roughly one-tenth of the recreational LSD dose. Microdosing has been alleged to increase productivity among those in the information technology industry (Solon, 2016), and a report on time perception changes induced by LSD microdosing has cautiously interpreted such findings as an enhancement of selective attention (Yanakieva et al., 2019). Greater visual acuity caused by an LSD microdose is reported by anecdote (Hawk, 2018)

and, at higher doses, in the literature (Carlson, 1958). Author Michael Pollan remarked the necessity for glasses can wane during some LSD experiences, the glasses becoming necessary only when the effects of the drug wear off (ITV News, 2019). These reported increases in visual acuity can be interpreted as real, and in need of explanation.

The "impaired sense of time" phraseology may also obscure the nature of that which is reported. According to a young woman who ingested 600 mcg LSD for a period of months:

> …time slowed so much that I could hear each individual rotation of the blades from the fan in the corner…(a)fter a few hours I regained function enough to manage to hit play on a laptop I'd set up next to me. Time was so distorted that, while I recognized the music, I felt nothing from it; by the time one note had played, I'd forgotten the last one. It no longer functioned like music to me. (Aella, 2017)

This slowing of auditory events, for example hearing each rotation of a fan, may include the slowing of speech, common to LSD reports, during which each spoken word seems far in time from the previous word or "slurred" (Liddell & Weil-Malherbe, 1953; Jaffe et al., 1973; Gawel, 1981). These are coordinate with the slowing of visual experience–the birds flying more slowly–or in the experience of one of the authors, a buzzing fly's normally blurred wingbeats becoming distinct. At this point, we shall argue:

- These altered perceptions are veridical, at least as veridical as perception can be, for perception is always an optimal specification of the external world.
- These effects–fans slowing, flies slowing–are timescale transformations of the specification of the external world, and a function of the chemical dynamics involved.
- The visual acuity changes are a natural, correlated effect.

- These are not hallucinatory effects, nor a function of the brain's generation of hallucinatory images.

Since these effects must scale with dose, approximate categories are:

- 10-50 mcg doses: at this level we shall argue there is straightforward perception: veridical but with the timescale transformation to be described.
- 50-250 mcg doses: at this level we shall argue the perceptual timescale specification is still veridical, however that the brain allows for increasingly more experience from the past–from what Bergson (1896/1912) termed "the virtual"–and that the perceptual timescale specification is still veridical but is increasingly divorced from possible action in the external world.
- 251-600+ mcg doses: at this level we shall argue there is very little correlation to possible action and veridical perception (please note, in the 600-mcg experience mentioned above by Aella, 2017, the perception of separate rotations of a fan would be considered veridical, however the overall conscious state of the subject seems flooded by her inner experience).

The Bergson-Gibson Model of Direct Perception

Without a theory of how the brain produces the image of the external world and, equally, how it "generates" internal images (if it actually does generate them), a subject matter like LSD that deals entirely with the transformations of images, or the experience of "strange" images, is certainly ungrounded. This is not far from theorizing how a radio "generates" newscasts spoken in French, or plays the Ninth Symphony or rock music, all inferred by a research method of breaking various tubes, flooding the radio with electricity, using a measuring device to see what "lights up," or other manipulations–when there is no concept of radio waves or broadcasting stations.

As noted earlier, the origin of the image of the external world is the "hard problem." If taken in the somewhat misdirecting terms framed by Chalmers (1995), namely in terms of "qualia," there is nothing in the image that is not qualia, including the multiple forms–tables, chairs, curtains, buzzing flies–that fill it. Indeed, Hardcastle's (1995) description of qualia was: "…the conductor waving her hands, the musicians concentrating, patrons shifting in their seats, and the curtains gently and ever-so-slightly waving…" (1995, p. 1).

Here we see *form* as qualia too, in fact, dynamically changing form, for all qualia exist only over time; all qualia are dynamic. We stress this to remove the static mindset that prevails on qualia and its examples–the "redness" of the sunset, the "whiteness" of the cauliflower–because LSD experience should have taught us that underlying even these seemingly static colors are extremely dynamic, vibrating fields. But the experiential image of the orchestra that Hardcastle is describing is entirely qualia, especially its dynamic, qualitatively changing forms–which are just as non-computable as the colors and sounds. It is the image of the external world that must be explained.[1]

We know that for Hardcastle's orchestral image there is no photograph of such in the brain. Neuroscience has progressed well beyond this conception that in some slice or area of the brain's neural mass itself, as though the neural mass is a photographic film, we can find something even vaguely resembling the image of an orchestra. Bergson (1896/1912), entertaining this question of the origin of the perceptual image, equally noted that no "photograph" of the external world is taken by or will be found in the brain, but he went further:

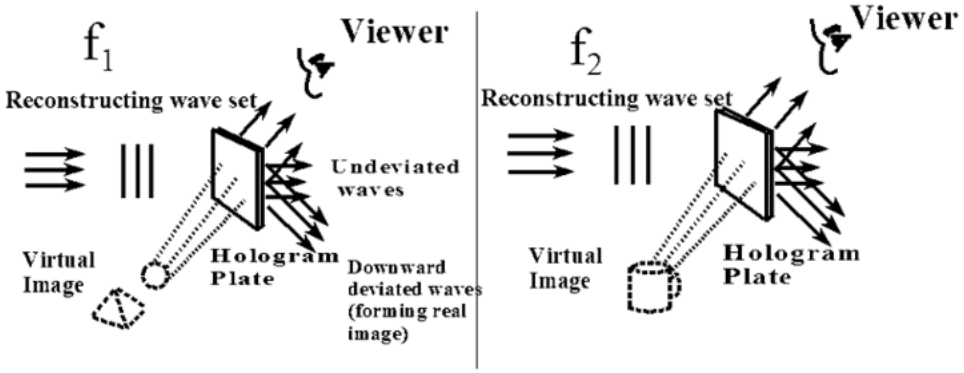
[1] Here we anticipate discussion of Bergson's model of time. "Gently" waving curtains, "mellow" violins, the soft redness of a sunset–these are functions of a continuously developing field, an indivisible development where, like a melody, each note or "instant" interpenetrates the next, and where the state of each is the reflection of the entire preceding series-an organic continuity. The computational model, predicated on discrete states where, as each current state is instantiated, the previous state no longer exists-cannot capture this organic development.

> But is it not obvious that the photograph, if photograph there be, is already taken, already developed in the very heart of things and at all points in space? No metaphysics, no physics can escape this conclusion. Build up the universe with atoms: Each of them is subject to the action, variable in quantity and quality according to the distance, exerted on it by all material atoms. Bring in Faraday's centers of force: The lines of force emitted in every direction from every center bring to bear upon each the influence of the whole material world. Call up the Leibnizian monads: Each is the mirror of the universe. (p. 31)

This was Bergson's declaration, 51 years before Gabor's 1947 discovery, that the universe is a holographic field, that at every point in the universe is the information for–the "photograph" of–the whole. But unlike Pribram (1971) or Bohm (1980), Bergson saw the brain as being (or creating, supporting) a modulated reconstructive wave passing through this holographic field (Figure 1). The neural processes–action potentials, neural spikes, etc.–seen currently as supporting "computations" become integral participants in the formation of this concrete waveform (Robbins, 2002).

Figure 1

Modulating the Reconstructive Wave



Note. The pyramid-ball or the cup are specified by precise modulation of the reconstructive wave from f_1 or f_2 (Robbins, 2006).

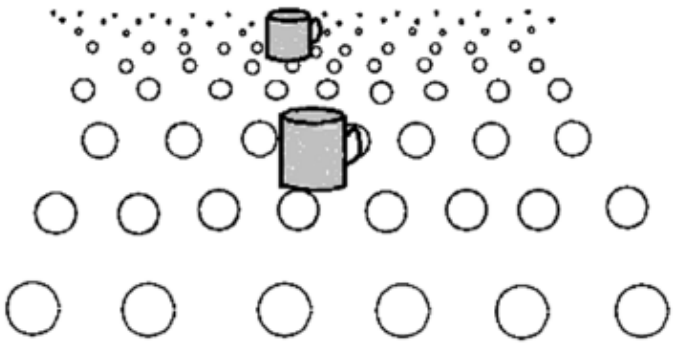
This brain-supported reconstructive wave is “specific to” a subset of the information within the holographic field (a vast field of interference patterning that is non-imageable) and the subset-specifying wave is effectively an “image” of a portion of the field (say, a coffee cup with stirring spoon).

Driving the modulating patterns of this wave are the invariance laws of Gibson (1966, 1979) which define these external events. For example, some of the information defining the event of stirring coffee is:

- A radial velocity flow field over the swirling surface.
- An adiabatic invariant (energy of oscillation/frequency of oscillation) relating to the periodicity of the spoon (Kugler & Turvey, 1987).
- An inertial tensor (Turvey & Carello, 1995) capturing the angular momenta of the spoon and defined over kinesthetic flow fields of the hand and arm.
- A texture gradient (Figure 2) defining the table surface and supporting, as one’s head moves, an invariant specifying the size constancy of the cup.
- Flow fields defining the form of the cup (Figure 3).

Figure 2

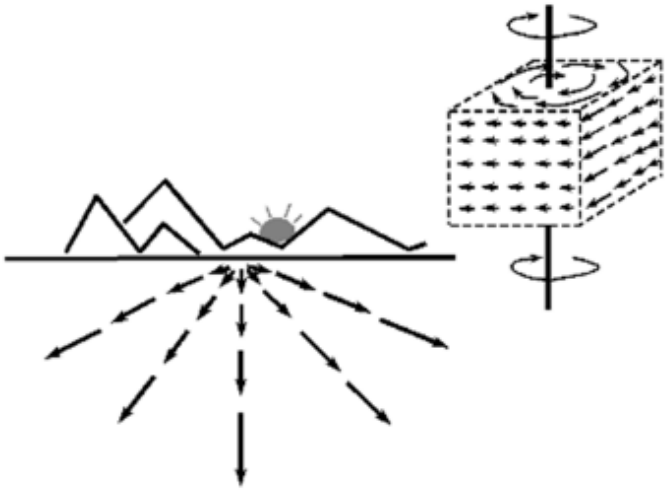
Texture Gradient



Note. The horizontal distance between texture gradient elements is $S_h \propto 1/d$. The vertical distance between texture gradient elements is $S_v \propto 1/d^2$. The size constancy of the cup moving across the gradient is an invariant, $S_c \propto 1/N$, as the vertical height over time is inversely proportional to the number of texture unit rows (N) occluded (Robbins, 2006).

Figure 3

Velocity Flow Fields



Note. Left, a flow field in which the velocity vectors increase inversely with the distance from the eye or $v \propto 1/d^2$. Right, the flow fields defining a "Gibsonian" Cube (Robbins 2004).

This "invariance structure" defined over the dynamic, ongoing event in the external field is driving/modulating the specifying reconstructive wave. Gibson (1966) argued this (invariance) information, e.g., the texture gradient of the table, is "specific to" distance and to the stretching-into-the-distance of the external environment (the table's surface), and that the brain is simply "resonating" to this information (i.e., there is no image within the brain). But to make sense of the (optical) origin of the image of the external world–the image of the coffee cup on the table,

e.g.–Gibson's "resonance" (1966) must be placed within Bergson's framework, i.e., the universe as a holographic field with the resonating brain effectively a reconstructive wave passing through and specific to an aspect or source within the field–now the image of the cup, swirling surface and stirring spoon.

What we have, thus far, is a model of direct perception, and direct realism. The coffee cup is precisely "where it says it is," within the field. It is not an image within the brain, nor in some mental sphere or dimension, nor is it "generated" by the brain. But this is not a naïve realism: the specified image, due to intrinsic uncertainties–one source of uncertainty, we shall see, residing in the nature of the flow of time–is always an optimal, i.e., a probabilistic specification of events within the field.

The Resonating Brain and the Quality of Form

The concept of an always "optimal specification" is critical for understanding both how there can be a direct but not a naïve realism, and how there can be illusions (which indirect realism seizes upon as proof that all percepts of the external world are like hallucinations generated only within the mind). The specification of form is illustrative.

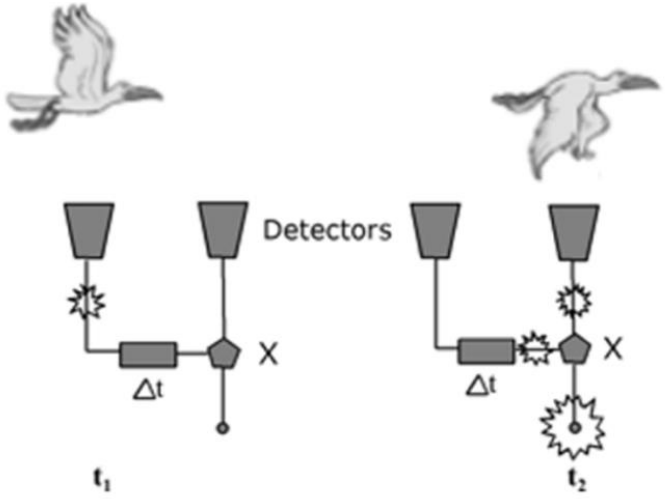
We can imagine a rotating cube, for which a series of cartoon frames of this rotation is created, slice by slice. If a computer program were tasked with computing this form as it rotates, examining frame after frame of the cartoon series, it would have to track the "features" of the cube–each vertex, the cube's edges–from frame to frame, i.e., it must track the correspondence of features from frame to frame to maintain the identity of the cube. This "correspondence problem" was eventually deemed intractable by perception theorists.

Current perception theory sees perceived form as derived from velocity flow fields (Figure 3) in conjunction with Bayesian constraints. Adelson and Bergen (1985) described a general class of low-level models based on linear filters known as "energy models," initially developed by

Watson and Ahumada (1983), for detecting the elements of dynamic form. These are addressed specifically to the detection of direction and velocity of motion, for example, as an edge of a cube transits the visual field. They are an evolution from the correlation filter (Figure 4) of Reichardt (1959) for motion and speed detection, and there are significant formal connections to it.

Figure 4

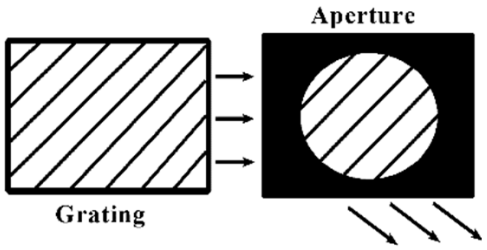
Reichardt Filter or Correlation Model



Note. The filter has two spatially separate detectors. The output of one of the detectors is delayed and the two signals are multiplied. The output is tuned to speed. Many detectors tuned to different speeds are required for the true speed of a pattern, and the difference of pairs of detectors tuned to different directions is taken (Reichardt, 1959; Robbins, 2004).

Figure 5

The Aperture Problem



Note. The card with the grating is moving to the right and passes beneath the card with the circular aperture. The ends of the moving lines are now obscured and only the downward motion of the lines is seen in the aperture (Robbins, 2006).

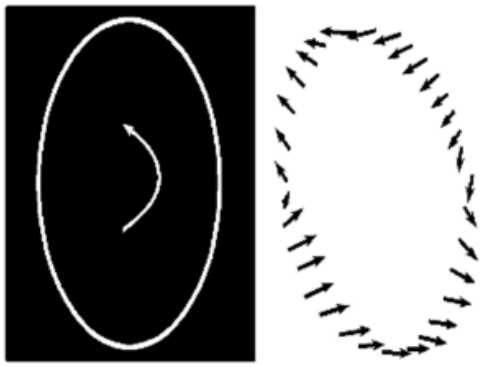
Another piece of background is needed: the receptive fields of the energy model filters are inherently "apertures" and thus, the velocities of the flow cannot be estimated with certainty due to the limited view of each field. Figure 5 shows the problem. The card with the lines is moving to the right, so the card and its lines actually have a horizontal velocity. But when the card passes under the limited aperture, and the ends of the lines are obscured, only a downward motion is seen. The aperture forces an intrinsic uncertainty in measuring the actual velocity of the lines. More generally, this indicates that measures of velocity by the visual system are intrinsically uncertain, as well. Therefore, the integration of multiple uncertain individual velocities must be inherently probabilistic. At this point of integration, Weiss, Simoncelli & Adelson (2002) inserted their fundamental, probabilistic (Bayesian) constraint, i.e., a probability estimate using a prior assumption about the nature of the world.

The fundamental constraint is "motion is slow and smooth." This takes form as simply a mathematical constraint in their Bayesian model, and this model explains a very large array of "illusions." Due to inherent measurement uncertainty, all perception, "veridical" or otherwise, must be viewed as an optimal percept based upon the best available information. For example, when applied to the velocity fields defining a narrow rotating ellipse (Figure 6), the violation of this "slow and smooth" constraint ends in the specification of a non-rigid, floppy object if the

motion is too fast (Mussati's illusion; Mussati, 1924). It is these constraints applied to the velocity flows, or their violation, that determine the rigidity of the form.

Figure 6

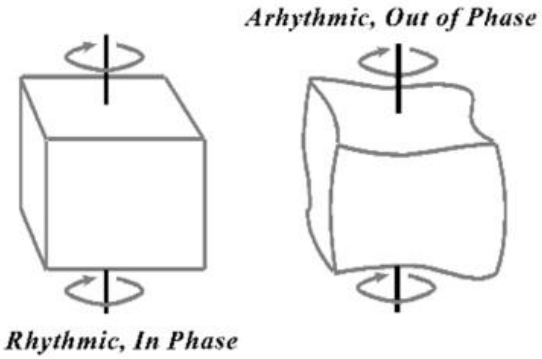
A Narrow Rotating Ellipse



Note. The normal velocity components (right) of the edge of a rotating ellipse (left). These tend to induce non-rigid motion (after Weiss and Adelson, 1998).

Figure 7

Rotating Cube



Note. The cube is strobed in phase with, or out of phase with, the symmetry period (Robbins, 2004).

If we were to consider a rotating "Gibsonian" cube, this form becomes a partitioned set of velocity fields. As each side rotates into view, an expanding flow field (Figure 3) is defined. As

each side rotates out of view, a contracting flow field is defined. The top of the cube is a radial flow field, and the "edges" and "vertices" (i.e., "features") of the cube are now sharp discontinuities in, or junctures of, these flows. The implications of this are revealed by a demonstration discussed in Shaw and McIntyre (1974) regarding a rotating, wire-edged cube (Figure 7).

A cube has a natural symmetry period of four–it is carried into itself every 90-degree rotation. Symmetry, it should be understood, is invariance; thus, an equilateral triangle would be carried into itself every 120-degree rotation, or a symmetry period of three. When the rotating, wire-edged cube is strobed in phase with or at integral multiple of its symmetry period, it appears, indeed, as a cube in rotation. But when strobed out-of-phase, it becomes a distorted, wobbly, plastic, or non-rigid object. In this wobbly "not-cube" case, the constraint (invariance) likely violated via the arrhythmic strobe is this: *a regular form displays a regular periodicity in time*. The strobe is essentially taking snapshots of the cube, yet these snapshots are not sufficient to specify the rigid cubical form one might expect; they are not sufficient to specify the straight lines, straight edges, corners, or vertices–any of the standard, static, geometric "features" of a cube.

In terms of how this plastically deforming cube can be an optimal specification of an object precisely within the external field, we can visualize the cube's rotation as a vastly spread-out four-dimensional structure consisting of a vast set of instantaneous, three-dimensional snapshots of the cube. From the perspective of an omniscient observer, no single three-dimensional snapshot fails to have perfectly straight edges, flat sides, and sharp vertices. However, the brain is not an omniscient observer; how this structure is ultimately specified by the brain–given it can only apply constraints to flowing fields–must have a degree of latitude. Likewise, we can view the precise specification of the pyramid-ball or the cup (Figure 1) via precise modulation of the reconstructive wave to f_1 or f_2. To an omniscient observer, who knows precisely

what interference patterns (object wave plus frequency of the original reference wave) are stored on the holographic plate, each specification is "correct." However, if a reconstructive wave that is a composite of f_1 and f_2 were beamed through the plate, now specified is a fuzzy pyramid-ball/cup "object" as the source of the wave front, i.e., an "illusion" (so to speak) relative to that which is stored in the plate, yet only illusory from the viewpoint of an omniscient observer.

Time in the Bergson-Gibson Framework

The plastically deforming somewhat-cube is therefore an optimal specification of transforming sources within an ever-transforming external field (Robbins, 2004). However, the nature of time transformation in this framework is a separate and deeper source of intrinsic uncertainty (Robbins, 2000, 2013, 2020). For explanation, a distinction must be drawn between the spatial or *classic* metaphysic–the framework for calculus and classical physics–and the *temporal* metaphysic of Bergson. At the base of the classic metaphysic is an abstract, infinitely divisible four-dimensional space of points as positions, in which time as the fourth dimension is an infinitely divisible dimension of instants, each corresponding to a point of an object in motion. In other words, the motion of an object from point A to point B is an infinitely divisible trajectory of points between A and B and their corresponding instances. However, this implies an infinite regress: between each pair of static, immobile points, a new line of points may be introduced, itself divisible to more points *ad infinitum*. To Bergson, this was an "absurd proposition that movement is made of immobilities" (1907).

Therefore, Bergson argued motion must be treated as indivisible (1896/1912). Or rather, when an object moves from point A to point B, the field is equally transforming indivisibly and, in equivalent terms, non-differentiably (Nottale, 1996). By this reasoning, transformation cannot be a series of discrete, static instants; and, given the fixedness of an instant concerning the cube, one can derive fixed, determinate values for the velocity of the cube. Or rather, at every interval of

time, no matter how minute, the cube is changing. If not, a static instant with determinate values would freeze not only the cube but the entire Universe (Lynds, 2003). This may be an elementary tradeoff: intrinsic uncertainty for change (Lynds, 2003).

The indivisibility of the holographic field's transformation implies a memory property–a form of primary memory–defined over the field's motion. In this indivisible motion, there are no "instants" falling into the past, thus into non-existence as the fly moves by and the spoon stirs the coffee. This property allows for the specification of the "past" reality, of an extent of the past transformation of the field (e.g., a portion of vast history of the wingbeats of the fly). All perception then is *already a memory*–a specification of the past of the external field. Yes, we again verge here on the source of the hallucination/illusion conception, but the specification, whether a rotating rigid cube, a wobbly kind-of-cube, or a buzzing fly--is an optimal specification of the external field's past and is as veridical and objective, though probabilistic, as possible.

Bergson's Panpsychism

Bergson's framework is a form of panpsychism, which maintains that perceptions are experienced as qualia and are not experienced by a Cartesian soul or Cartesian subject of consciousness. The holographic field, where the state of each point/instant (at the most minute possible scale of time) reflects the states of all other points, has then a very elemental awareness defined across the whole. Because the field is transforming indivisibly, an elementary property of memory is defined across it, as well. The brain can then be seen as specifying a timescaled form of this elementary awareness from a specific spatial perspective (that of the body). At the null scale of time, the body is not truly distinct in the field from, say, a fly. As successive scales are specified–fly as a cloud of electrons, then a motionless, crystalline, vibrating being, then a heron-like being slowly flapping its wings, then a buzzing, blurred-wing being of normal scale–subject is differentiating from object, and the meaning of Bergson's principle is clarified: "Questions relating

to subject and object, to their distinction and their union, must be put in terms of time, rather than of space" (1896/1912, p. 77).

And unlike Bergson's panpsychism, traditional panpsychism suffers from the "combination problem" (Chalmers, 2016). If the material-field consists of tiny, proto-conscious "particles," then how does an aggregate of such particles combine–whether in microtubules, in the neurons, in the mental, or in "somewhere"–to form the experience (the dynamic image) of the coffee cup, the swirling liquid surface, the stirring spoon, the buzzing fly, and all at a particular scale of time? Panpsychism, unmodified, has no mechanism to explain this image. When the brain is seen as a reconstructive wave passing through this (panpsychic) field, specific to a source at a scale of time, the panpsychic framework now has a dynamic mechanism for explanation.

Perception and Scales of Time

Gibson (1966) invoked a resonance conception of the brain because he saw that the neural mass is required to be something like "resonating" over these flows, whether the eyes are darting back and forth, isolating invariants, or whether the field itself is transforming like the rotating cube. Just as the edges and vertices of the cube are simply discontinuities in these flows, i.e., they are invariants that cannot exist as "features" in a static instant, but only over these (continuous, indivisible) flows, there cannot be static "bits" of information flowing along neurons, either. Rather, there must exist a resonating mass over which these invariants can exist, or equally, which is supporting or reflecting the invariance structure of the external event. In Bergson's framework, this "resonance" comprises a very concrete and dynamic reconstructive wave. Importantly, this is not an *abstract* wave or resonance, such as a dynamical systems characterization with attractors; by concrete we mean as concrete as the vibrations of a metal plate upon which complex sand patterns are formed, as concrete as the vibrations of the wood of a guitar, and as concrete as a wave of light that passes through a holographic plate.

In this concrete model of the brain, where the biological mass forms a reconstructive wave, biochemical dynamics must play an intrinsic role in the specification of the external world. Underlying these dynamics (and the wave they create) are chemical velocities, and these determine the *scale of time* at which an image is specified. The concept of chemical velocity is expressed in one form by the Arrhenius equation (Laidler, 1996):

$$k = Ae^{(-E_a/RT)} \quad (1)$$

Here *A* is a constant, *R* is the universal gas constant, *T* is the absolute temperature, and E_a is the activation energy or rather, the minimum energy required to initiate a chemical reaction. An increase in temperature raises chemical velocity, and Hoagland (1966) noted the slowing of experienced time is common to fevers. The temperature dependence of neural conduction velocities is common to many species (Yu, Hill, & McCormick, 2012; Fillafer & Schneider, 2013), and temperature effects are among the physiological changes induced by LSD (Clark, 1987). These effects include hyperthermia (Liskow, 1971; Hashimoto et al., 1977), and a biphasic effect by which LSD lowers temperature for a short period, then increases temperature and sustains it above baseline for a matter of hours (Rodriguiz et al., 2021).

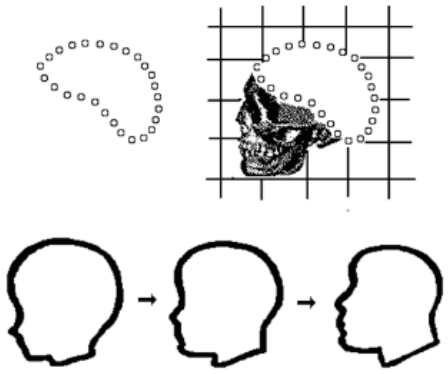
At our normal scale of time, a fly is seen as “buzzing”, and its separate wing beats–of which there are roughly 200 per second–are indistinguishable. Presume, as proposed by Hoagland (1966), that a catalyst were introduced for the slowed experience of time in the context of Equation 1. As the chemical velocity increases, the wingbeats of the fly would slow gradually, become distinguishable, and at some point, the fly would be perceived as flapping its wings like a heron. Such a principle would also hold for the blades of a fan or for the sounds of a sentence, mentioned above.

We should note this is already an in-principle question. That is, if simply a change in temperature can alter the dynamics of a system, would Nature not have had to allow for this? This points to the significance of Gibson's invariance laws in perception: in relativity, physical laws are invariance laws; they are invariant to changes in the space-time partition. The same law for distance (d =vt) holds in either S, the stationary system, or in S', the moving system (d' = vt') with its altered space and time units. So too, in changes of the perceptual spacetime partition, it must be invariance laws–laws that hold in all partitions–that specify perceived events.

As an example, the aging of the facial profile is a "slow" event in our normal scale of time. The aging is specified by a strain transformation applied to a cardioid form fitted over the skull (Figure 8). The same law (strain/cardioid) would apply if the aging were sped up, say, to a head very rapidly transforming, and the law (information) would be utilized by the action systems to modulate the hand to grasp the rapidly changing head.

Figure 8

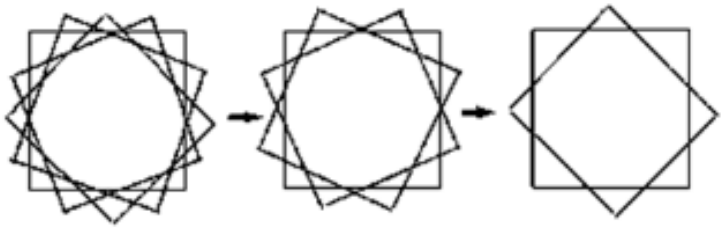
Aging of the Facial Profile



Note. A strain transformation is applied to a cardioid fitted over the skull. A few of the facial profiles generated along the aging dimension are shown (Adapted from Pittenger and Shaw, 1975).

Figure 9

Rotating Serrated-edged Cube



Note. Transitions of a cube through serrated-edged figures of 4N-fold symmetry (Robbins, 2006).

Take a cube and spin it increasingly faster. When viewed from above (Figure 9), the edges will pass through a series of serrated figures with 4N-fold symmetry (8-edged, 12-edged, 16-edged, etc.) and finally unto a spinning cylinder with a fuzzy haze of infinite symmetry. Starting from this spinning cylinder, the opposite would be affected by introducing a catalyst of the relevant kind, and the cylinder would reverse through successive figures of 4N-fold symmetry (the invariance law) and finally, with sufficient catalyst, to a motionless 4-sided cube. The cylinder/cube, under the effect of the catalyst, is specified according to an invariance law, and this has nothing to do with an "illusion" or hallucination.

The Reichardt filter (Figure 4) was an early model for the detection of motion concerning this line of conceptual development (i.e., velocity flows) represented by Weiss et al. (2002). Its simple structure is convenient to frame this starting point of the perception of form and its relation to time. Each half of the Reichardt filter is tuned to a particular velocity dependent upon Δt (Figure 4). If the receptive fields of two detectors were one centimeter apart, and Δt set to one second, then the filter would detect an object moving at one centimeter per second, but not at five centimeters per second or at a half-centimeter per second. Of course, any analogy between the Reichardt filter and the human visual system would require a large array of these filters, tuned to a spectrum of different speeds and oriented to many directions.

Via the Reichardt filter analogy, the beating wings of a fly (at 200 cycles per second) would sweep up and down a particular detector-pair tuned to the velocity of the wings (in the downward direction). Another detector pair would be needed, oriented to the upward direction, to register the reverse motion of the wings. If some rate of firing of the detectors were assumed, such as 10 firings per second, due to constraints on their chemical bases, the wings of a fly may appear as a blur.

However, if the detectors' rate of firing were increased to 50 firings per second, or to 100 firings per second, such that the wings of a fly were distinguishable, then in these cases the fly may appear like a heron. These increases (firing rates, conduction velocities, etc.) would be required not only in the detector "neurons" but also along the paths which comprise at least the visual motor system, so that no bottlenecks are encountered (a "bottleneck" being, for example, signals at 200 per second arriving at some processing node set at 10 per second). Whether and how LSD can increase rate processes on this timescale are empirical questions, and the following sections describe a method to answer them.

A Biochemical Framework for the Bergson-Gibson Model

An overview of the biochemical framework for the Bergson-Gibson model, described in this section and the next, is:

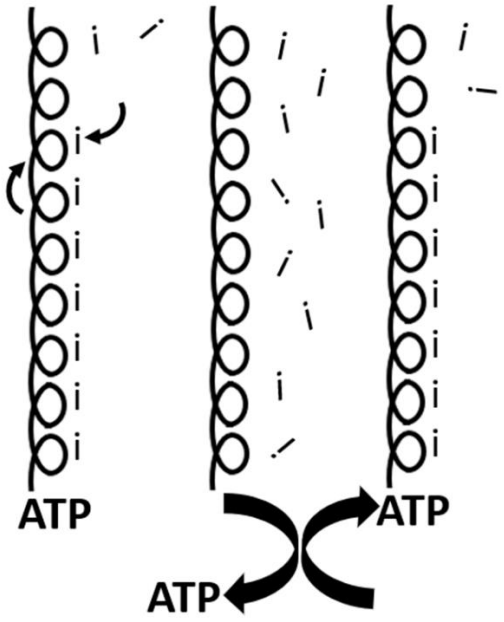
- Near-equilibrium thermodynamics are an emergent context for the action potential (Heimburg, 2017), for biochemical oscillations (Thoke et al., 2018), and are proposed to be relevant to cognition (Perez Velazquez, Mateos, & Guevara Erra, 2019). This perspective challenges the prevailing view of highly dissipative cellular processes.
- The influence of an effector, such as LSD, upon the cooperative interaction of many other ions and molecules near-equilibrium, is

described by Gilbert Ling's association-induction hypothesis (Ling, 1984). A simple cartoon model is shown in Figure 10.

- We propose that LSD, by way of an electronic inductive effect, imparts a small quantity of energy to the near-equilibrium dynamics of the brain. According to the association-induction hypothesis, and by way of LSD receptors, this manifests as large changes to cooperative behavior and therefore, changes to rate processes on the relevant timescale.

Figure 10

Biochemical Oscillations and Cooperative Adsorption



Note. Left, a cartoon polymer onto which species *i* is adsorbed in the presence of ATP as the "cardinal" adsorbent. The adsorption is "cooperative" or rather, by way of a next-neighbor effect (small arrows), successive adsorptions proceed away from the cardinal adsorbent. The polymer may interact with no cardinal adsorbent (middle) or with an alternative cardinal adsorbent, such as ADP. For simplicity, other adsorbed species are

not shown, and the cartoon does not describe conformational changes to the middle polymer in the absence of ATP. Because the *i's* become upright when adsorbed, the orientation of *i* would represent a quantifiable physical state exhibiting periodicity. The time moving from the cartoon on the left to the cartoon on the right, in the recurrent presence of ATP, represents the period of oscillation.

Several observations appear consistent with the hypothesized increase in rate processes. These include: the aforementioned temperature changes that are straightforwardly related to conduction velocity, the repeated observation of an alpha wave frequency increase by LSD (Fink, 1969; Carhart-Harris et al., 2016), an increase in the frequency of model nervous systems by LSD (Wright, Mocrhead, & Welsh, 1962), the enhanced release of the glutamate by LSD and subsequent increase in the frequency of EPSPs and EPSCs (Muschamp et al., 2004), the promotion of social behavior by LSD that requires excitatory neurotransmission but not inhibitory neurons (De Gregorio et al., 2021), and an increase in specific and nonspecific currents by LSD in neuronal cultures (Aghajanian & Lakoski, 1984; Parker, Panicker, & Miledi, 1990; Garratt, Alreja, & Aghajanian, 1993). The alpha wave frequency increase is particularly compelling, as the 10 hertz rhythm is deemed to be a "fulcrum" (Garcia-Rill et al., 2016) or carrier wave for the brain and is scaled with temperature (cf. Garcia-Rill et al., 2016, plus above example by Hoagland, 1966). Because frequency and amplitude are inversely related, the alpha wave frequency increase is usually contextualized as a loss of power (Carhart-Harris et al., 2016; Swanson, 2018).

Recently, several reports have suggested that the action potential (Heimburg, 2017), biochemical oscillations (Thoke et al., 2018), and cognition (Perez Velazquez, Mateos, & Guevara Erra, 2019) may profit greatly from the perspective of near-equilibrium thermodynamics, by which low energy inputs are able to sustain and affect properties that are scale independent (such as, global oscillations). From this perspective, it is important to recognize that living tissues are

colloidal–i.e., responsive hydrogels with an ordered cellular interior–and therefore can resist thermal randomness to an extent not generally appreciated (for review: Bagatolli, Mangiarotti, & Stock, 2021). A helpful example is that of a pendulum or a clock, which can oscillate due to its rigidity of form (Thoke et al., 2018), or oscillations in gelatin which share similarities with the normal human alpha rhythm (Adams, 2010). This notion of living tissue as a gel-like network, operating near-equilibrium, is relevant to the thermodynamic properties which govern the neural impulse (Drukarch et al. 2018), and to the influence of LSD over bulk-phase dynamics such as the disappearance of the nucleolus (Gayer & Príbys, 1970), the migration of melanin granules (Kemali, Milici, & Kemali, 1983), and the assembly and stabilization of microtubules (van Woerkom, 1990; Lew, 1995).

Seeking a general principle of coupling, several recent reports have applied or referred to Gilbert Ling's (1984) association-induction hypothesis (Thoke, Bagatolli, & Olsen, 2018; Thoke et al., 2018; Begarani et al., 2019; Olsen, Stock, & Bagatolli, 2020). The association-induction hypothesis is a statistical mechanical model for the cooperative adsorption of ions, water, and other molecular species near-equilibrium, under the control of a smaller number of "cardinal" adsorbents (Figure 10). For example, a single molecule of the cardiac glycoside ouabain, as a cardinal adsorbent, can affect the adsorption potential for over 1,000 amino acids (Ling, 2012). Ouabain can also affect the extent of water relaxation in living cells dramatically (Olsen, Stock, & Bagatolli, 2020). We propose that LSD functions as a cardinal adsorbent, generating cooperative interactions and therefore, changes to rate processes on the relevant timescale (i.e., that of the Reichardt filter analogy), thereby tying the "concreteness" of biochemistry to our perceptual model.

In contrast to familiar enzyme kinetics grounded in the law of mass action and active conformations, the Yang-Ling adsorption isotherm is informed by next-neighbor interaction

energies and is general (Ling, 1984; Thoke, Bagatolli, & Olsen, 2018). Or rather, the isotherm recapitulates non-cooperative as well as cooperative effects, such as the binding of oxygen to hemoglobin that is usually described by the Hill equation (Ling, 1984). Recently, the Yang-Ling isotherm was found consistent with the kinetics of glycolytic enzymes in high concentrations of polyethylene glycol, presumed relevant to the cell's crowded, gel-like interior (Thoke, Bagatolli, & Olsen, 2018). The isotherm is (Ling, 1984):

$$[\mathrm{p_i}]_{\mathrm{ad}} = \frac{[\mathrm{f}]}{2}\left[1+\frac{\mathrm{e_0}-1}{\sqrt{(\mathrm{e_0}-1)^2+4\mathrm{e_0}\exp(\gamma/RT)}}\right] \quad (2)$$

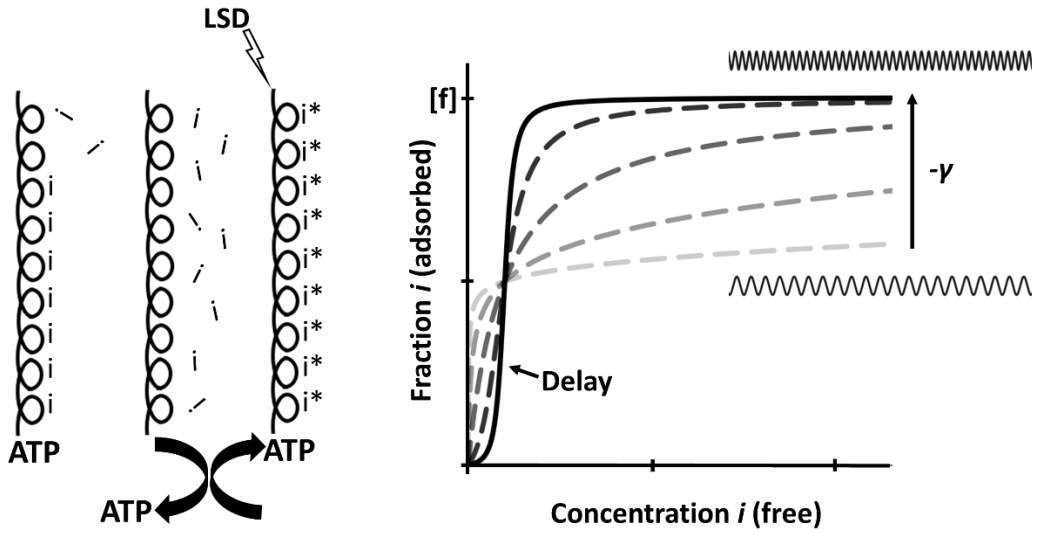
Here $[\mathrm{p_i}]_{\mathrm{ad}}$ is the concentration of the *ith* species adsorbed onto [f] number of sites, as opposed to an alternate species *j*. *R* and *T* are the universal gas constant and absolute temperature, respectively, and γ is the important next-neighbor interaction energy or rather, the free energy required to create one mol of *ij* neighboring pairs such that a change from *iii* → *iji* entails an energy of -*γ* (Ling, 1984). Notably, the ultimate term of the denominator is of the same form as the activation energy in Equation 1, and 5-HT receptor binding requires the cost of such a barrier (Noller, Kienzl, & Riederer, 1982). $\mathrm{e_0}$ is the concentration ratio of nonadsorbed *i* and *j* in solution with the relevant, adsorbing macromolecule, multiplied by their intrinsic equilibrium constant *K* (Ling, 1984):

$$\mathrm{e_0} = \frac{[\mathrm{p_i}]_{\mathrm{free}}}{[\mathrm{p_j}]_{\mathrm{free}}}K \quad (3)$$

The exchange of one cardinal adsorbent for another, such as ATP for ADP (Ling, 1984), or in this case serotonin for the other 5-HT receptor analogs, may shift the next-neighbor interaction energy in Equation 2 from γ to γ_c, where γ_c is the next-neighbor interaction energy in the presence of the new cardinal adsorbent. Such an exchange may also shift the intrinsic equilibrium constant in Equation 3 from K to K_c, where K_c is the intrinsic equilibrium constant in the presence of the new cardinal adsorbent. In some cases, the replacement of one cardinal adsorbent by another will lower γ in Equation 2 to the extent that the system becomes autocooperative, i.e., each adsorbed species of a particular kind increases the probability of further adsorption for that species. A general scheme of this proposal in relation to LSD is shown in Figure 11.

Figure 11

The Biochemical Framework Proposed



Note. Left, a cartoon polymer onto which species *i* is adsorbed in the recurrent presence of ATP. The addition of LSD, by way of an electronic effect (lightning bolt), and its relatively long residence time (Wacker et al., 2017), is proposed to lower the next-neighbor interaction energy along the polymer, described by the parameter *y* in Equation 2. Under the influence of LSD, a greater fraction of *i* is absorbed. For simplicity,

other important adsorbed species, such as *j* in Equation 3 or serotonin, are not shown. Right, theoretical curves for the fraction of *i* adsorbed onto [f] number of sites, calculated according to Equation 2. The solid curve on the graph corresponds to the most negative value of *y* in Equation 2, and to the autocooperative adsorption of *i*. The dashed curves correspond to more positive values of *y*. Each curve may reflect an oscillatory frequency in the physical state of *i* (sine waves), represented by the orientation of *i* or by the presence of an asterisk in the cartoon, and defined by the parameter *h* in Equation 4. The cartoon is general in nature and is not intended to imply that LSD receptors are regulated directly by ATP. The graph was adapted from Ling (1984) and was produced in Desmos (2020).

Furthermore, *i's* and *j's* may be considered metals of the neural impulse and, importantly, models of ion adsorption at equilibrium are formally equivalent to conventional treatments of the transmembrane potential (Ling, 1984; Tamagawa & Ikeda, 2018). For this reason, action potentials may be conceived as "all or none" adsorption processes (Ling, 1984), or as electrochemical pulses for which selective ion permeabilities are not required (Heimburg & Jackson, 2005; Heimburg, 2017). Minimally, this would allow for the reinterpretation of LSD- and serotonin-induced potassium conductance when implied by the Nernst equation (Aghajanian & Lakoski, 1984). More generally, this allows for the tying of many and ostensibly unrelated observations into a coherent biochemical framework. For example, the observation that LSD dramatically reduces inward calcium currents and increases rectifying potassium currents in central neurons (Penington & Fox, 1994). LSD imparts a similar effect to an unrelated model system (Parker et al., 1990), and these data would appear difficult to generalize to any scale independent perceptual model. Given the association-induction hypothesis, however, these data–as well as the observation of enhanced glutamate release–may be interpreted as arising

from a cooperative transition toward an “efficient,” “potassium-loving” condition of the cell-as-a-hydrogel, consistent with changes to perception (Peat, 1975). Or rather, by way of Equation 2, the cardinal adsorbent regulates the “state equilibrium” (Peat, 1975) between different phases of a gel, each with peculiar rate processes. Here, a helpful analogy can be drawn to sound, and the dependence of its speed upon the compressibility of the medium though which it travels.

By the association-induction hypothesis, the temperature dependence of conduction velocities is a stochastic process by which sequential adsorptions occur “much more rapidly” at higher temperatures (Ling, 1984). While this implies dissipation for the near-equilibrium regime, oscillatory behavior would still occur in a critical region, whether as observed by experiment (Thoke et al., 2018) or as implied trivially by the propagation of brainwaves during the LSD experience. Regarding the latter, the cooperative formation of molecular ensembles was recently highlighted for having important parallels to the relation between dissipation, compartmentalization, and cognition (Perez Velazquez, Mateos, & Guevara Erra, 2019). The association-induction hypothesis may ground this proposal, as well as the recent finding that temperature dependence of sleep spindle frequencies is due largely to local biophysical mechanisms rather than to global modulation (Csernai et al., 2019). For cell cultures to which LSD was observed to impart a depressive effect (Wei & Chiang, 1986; Aghajanian & Marek, 1999), these phenomena can be attributed to adsorption potentials that are peculiar to the surface proteins of those systems, or to a state-equilibrium that is peculiar to experimental conditions (Ling, 1984). In general, the recognition of individuality among living cells in terms of their surface adsorption potential or other bulk-phase, physical properties–and, according to their normal functions or to their position in a developmental gradient–is an impetus for the association-induction hypothesis as opposed to less-generalized biochemical mechanisms (Peat, 1975).

Sequential, autocooperative processes are characterized partially by a delay before the achievement of full effects (Figure 11). Several features of LSD biochemistry appear to meet this criterion, including the glycolytic activity among brains on LSD (Torre & Vergani, 1969), the slow onset of LSD-induced excitability compared to serotonin (Garratt, Alreja, & Aghajanian, 1993), and the biphasic temperature response mentioned above. Such a delay is also consistent with an increased effect of LSD at higher temperatures and little to no effect at lower temperatures (Aghajanian & Weiss, 1968; Heikkila & Brown, 1979), and with low-concentration effects, for a billionth of a gram LSD per gram of nervous tissue produces a ten-hour experience (Freedman & Boggan, 1982). However, our hypothesis does not require that LSD generates specifically autocooperative behavior in all systems. For example, the actions of LSD may include relief of a relatively noncooperative state induced by serotonin, for which LSD was long believed to exert its main effect as an antagonist (Roddy, 2013).

Oscillations in the physical state of an adsorbed species (Figure 12) may be described by part of the model for the dipolar-relaxation of water in phase with the activity of glycolysis (Thoke, Bagatolli, & Olsen, 2018):

$$\frac{dh}{dt} = v_0 - k_1 h \tag{4}$$

Here h is some quantifiable physical state for an oscillating species, k_1 is a first-order rate constant, and v_0 is (Thoke, Bagatolli, & Olsen, 2018):

$$v_0 = V[\mathrm{L}]_{\mathrm{Bound}} \tag{5}$$

Here *V* is the velocity maximum of an oscillatory regime (an enzyme, repeated action potential, etc.) and the multiplicand is the concentration of the relevant cardinal adsorbent that is bound (ATP, LSD, etc.). In the full model, *V* and the concentration of bound ligand are some further function of *h* and of temperature, and these were coupled to the activity of glycolysis (Thoke, Bagatolli, & Olsen, 2018). For our purposes, the curtailed model is shown to describe that if, for example, *h* were the chemical potential of the lipid membrane in which the 5-HT receptors are present, Equation 5 would change accordingly, for the affinity of serotonin to its receptor is influenced by membrane fluidity and by the physical state of membrane-associated waters (Heron et al., 1980; Postila & Róg, 2020). This simple model would need adusted depending on the rate processes of interest–for example, changes to the frequency of GCPR-induced calcium waves (Grundmann & Kostenis, 2017) in relation to any of the thermodynamic variables mentioned above.

Therefore, a clear experimental aim would be determination of fluorescence dynamics for the dipolar-relaxation probes 6-acetyl-2-dimethylaminonaphthalene (ACDAN) and 6-lauroyl-2-dimethylaminonaphthalene (LAURDAN) coincident the known molecular effects of LSD. These probes reveal a comprehensive profile for the dipolar relaxation of water in the cytoplasm and of waters associated with lipid membranes, respectively (Bagatolli & Stock, 2016). Additionally, since the heat capacity of living cells is mostly that of its water, and therefore temperature changes are reported indirectly by ACDAN (Thoke et al., 2018), this aim could provide a circumstantial relation between the framework proposed and the biphasic temperature response observed (Rodriguiz et al., 2021).

Perhaps the most visible progress concerning LSD mechanism is the work of Wacker et al., (2013) who characterized structural features important for β-arrestin signaling at the 5-HT_{2B} receptor (5-HT_{2B}R). These data were extended, first via modeling and recruitment assays (Wacker

et al., 2017), and second via crystallography (Kim et al., 2020), to 5-HT_{2A}R that is essential for LSD's experiential effects (Preller et al., 2019). The recruitment assay of these reports made use of human cell lines expressing the relevant constructs (Wacker et al., 2013), and we hypothesize differential solvent dynamics for the effect (as measured by spectroscopy of ACDAN or LAURDAN, and as compared to assays coincident with unbiased signaling or to assays treated with serotonin). In principle, this type of experiment could be extended to neuronal cultures and with the use of raster image correlation spectroscopy (RICS) for the determination of solvent dynamics on the microsecond timescale (Begarani et al., 2019).

Also, experimenters should determine longer (>48 hour) effects of LSD in the context of membrane potential and ion balance. Ling (1984) described an experiment in which hysteresis was observed in muscles treated with ouabain or rather, resting membrane potential and potassium balance changed indefinitely after exposure to the drug was stopped. In the context of the association-induction hypothesis, this experiment represents the power of ouabain over next-neighbor interaction energies (Ling, 1984). Because relatively long-term behavioral changes are observed from a single LSD dose (Alper et al., 2018), it is tempting to suppose at least some of the LSD fingerprint persists, biochemically, long after the psychedelic experience subsides. To the best of our knowledge, no report has looked specifically at membrane potential or ion balance on this timescale (>48 hour) and in this context. Here, relevant observations include the decreased binding affinity of serotonin–even at higher concentrations–after daily administration of LSD (Lee & Geyer, 1980; Buckholtz, Freedman, & Middaugh, 1985), and the "very slow" reversal of LSD-dependent frequency increases in model systems (Wright, Moorhead, & Welsh, 1962).

As mentioned, the Yang-Ling isotherm is "general" and describes noncompetitive interactions as well as competitive interactions. Therefore, not only an exchange of cardinal adsorbents but different concentrations of a single cardinal adsorbent may influence system

dynamics dramatically (Ling, 1984). As the concentration of LSD rises, the hypermetabolism reported in the study of other psychedelic drugs (Vollenweider et al., 1997), and implied by the increased temperature and CBF mentioned above, would lead to a decrease in the cardinal adsorbent ATP and its governance over the near-equilibrium state. This may be a confounding variable for the model proposed or, more generally, for the study of LSD.[2]

Electronic Induction and the Inductive Index

The framework above depends on a relatively long-range electronic effect induced by LSD and propagated via receptor proteins (Ling, 1984; Begarani et al., 2019). Or rather, the "induction" aspect of the association-induction hypothesis is the physical mechanism by which *γ* in Equation 2 is lowered (Figure 11). For example, in the case of metabolic oscillations in yeast (Thoke et al., 2015) or in human lysozomes (Begarani et al., 2019), it is the "inductive effect" of ATP, transmitted through proteins and via the mechanism explained below, which polarizes water and therefore, resists thermal randomness, keeping the system in a gel-like state and near-equilibrium.

Importantly, the fluorescence spectrum of LSD shifts when bound to its receptor–but not to controls–implying that delocalizations of electrons are coincident effects (Shih & Roh, 1977). Though early reports indicated a strong correlation between the subjective effects of psychedelic compounds and their electron orbital energies (Snyder & Merril, 1965; Kang & Green, 1970; Domelsmith & Houk, 1978; Domelsmith, Munchausen, & Houk, 1978), to the best of our knowledge, the import of these data remains unknown. In contrast, it is usually the *independence*

[2]Here we note what surely must be an enormous variability in the glycogen status and other energetic parameters among LSD users. While the effects of LSD are often compared to mental disorders or are often discussed in the context of a "bad trip," to the best of our knowledge only a small number of researchers have attempted to make these phenomena distinct in terms of the energy status of the organism (Peat, 1975; Roddy, 2013).

of structural and chemical features among these drugs that is considered most relevant for modern proposals of biochemical mechanism (Perez-Aguilar et al., 2014).

Regarding transmission through proteins, the "inductive index" of Chiang and Tai (1963)–an *ab initio* method for the quantification of electronic inductive effects–was recently adapted for R groups of 15 standard, non-aromatic amino acids (Lara-Popoca et al., 2020). For example, the methyl group of alanine is "electron donating" to its alpha carbon and the ε-amino group of lysine is "electron withdrawing" (Table S1; Figure 12). Inductive effects are foundational to organic chemistry, and the inductive index was found consistent with a variety of chemical data, including the dissociation constants of oxygen acids and metallic hydroxides (Ling, 1984). Furthermore, inductive index values calculated according to the modified algorithm of Lara-Popoca et al. (2020) were found highly correlated to fluorescence lifetimes in tetrapeptides and to the ionization constants of the standard amino acids. In peptides, a relatively long-range transfer of electron density is a mechanism proposed for pK_a changes that scale with length (Ling, 1984) and with phosphorylation (Manning & Manning, 2018).

Ling (1984) proposed that primary sequence analyses of the inductive index would reveal long-range electronic characteristics that are important for the association-induction hypothesis. Because missing values for the aromatic amino acids can in theory be interpolated from their respective alpha amino pK_a (Lara-Popoca et al., 2020), we determined a modified inductive index for all 20 of the standard amino acids (Table S1). Therefore, our analysis below depends also upon an extrapolation from the relatively high pK_a of proline's secondary amine to a relatively strong inductive effect (Table S1). This, and a previous quantification of proline's inductive effect (Dwyer, 2005), are considered in the supplementary information.

Given the relative strength of electron donating R groups (Table S1), and their preponderance in the human genome and among high affinity LSD receptors (Table 1), sequences

enriched with electron withdrawing R groups are of interest. Among amino acids in the primary sequence of 16 high affinity LSD receptors, 5-HT_{2A}R was found to have the highest mean inductive index and to be the most enriched with electron withdrawing R groups (Table 1). Given that 5-HT_{2A}R is the common target of all psychedelic compounds (Perez-Aguilar et al., 2014), we interpret the electron withdrawing character of its amino acids–in contrast to the other high affinity LSD receptors–to be an important distinction.

Table 1

Primary Sequence Analysis of the Inductive Index in High Affinity LSD Receptors

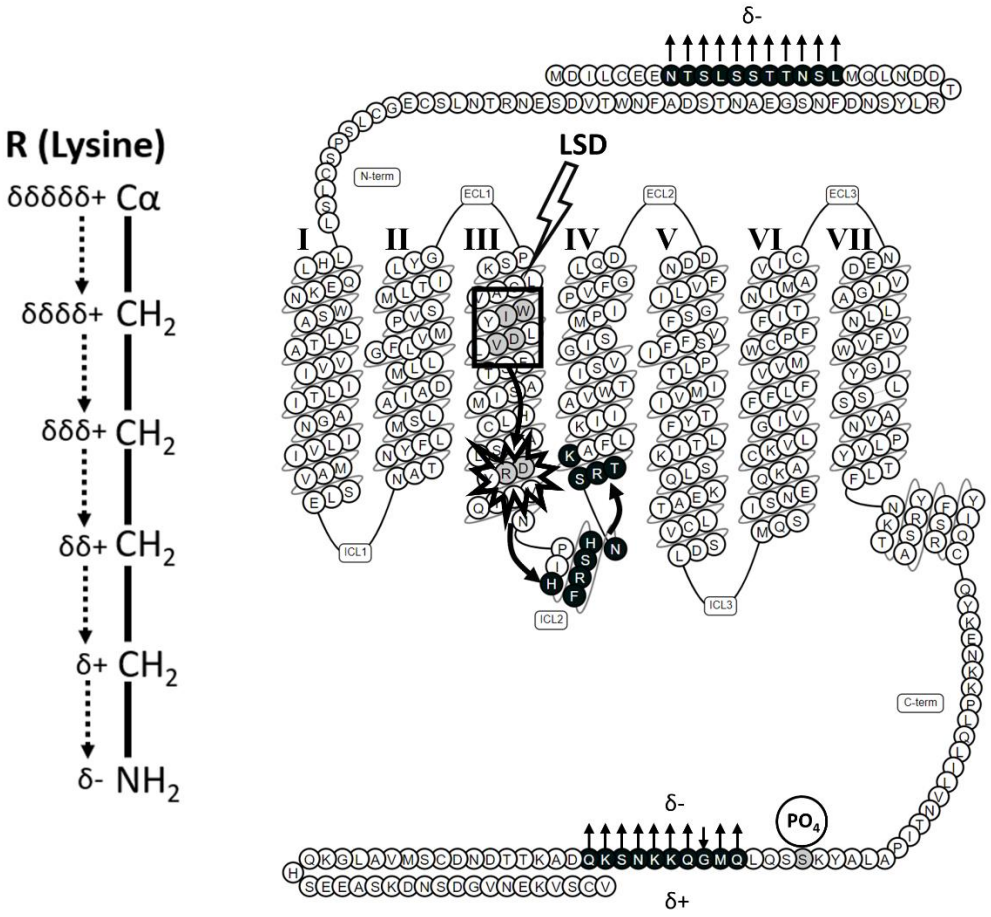
Protein	Amino Acids	Mean Inductive Index	Proportion EWG	Significant Regions
	LSD Receptors			
5-HT_{1B}R	390	-47.7	.431	0
5-HT7R	479	-53.52	.413	0
5-HT6R	440	-72.2	.359	0
5-HT_{1A}R	422	-51.9	.4	0
5-HT_{1D}R	377	-40.2	.432	0
5-HT_{5A}R	357	-42.0	.434	2
D3	400	-43.2	.448	0
5-HT_{2C}R	458	-44.1	.426	0
Alpha-2AR	465	-62.9	.385	0
5-HT_{1E}R	365	-36.2	.471*	1
D4	419	-96.2	.303	0
D2	443	-40.7	.476*	1
D1	446	-42.9	.444	0
D5	477	-54.1	.403	0
5-HT_{2B}R	481	-32.0	.47*	1
5-HT_{2A}R	471	-28.3	.48**	3
	Totals			

LSD Receptors	6,890	-49.4	.423	8
Human Proteome	Unknown	-44.5	.444	Unknown

Note. Primary sequences were obtained from UniProt (The Uniprot Consortium, 2021) and their accession number is listed in Table S2. “EWG” refers to amino acids with electron withdrawing R groups (Table S1). The distribution for the inductive index is multimodal (Shapiro-Wilk p: <.001) and a binomial test was performed regarding the proportion of EWG in each protein (JASP Team, 2020). The alternative hypothesis was that the proportion of EWG in each protein was greater than .423. An asterisk represents p<.05 and two asterisks represent p<.01. “Significant regions” refers to distinct regions of the primary sequence enriched significantly (CL>95%) with electron-withdrawing R groups, calculated according to the significance test of Karlin and Altschul (1990), and detailed in the supplementary information. The human proteome values were extrapolated from the probability of amino acid occurrence in the Human Genebank (Shen et al., 2006; NCBI Build Number 34, March 2004).

Figure 12

Proposed Inductive Effects in 5-hydroxytryptamine Receptor 2A



Note. Left, the inductive effect of the primary amine in the R group of lysine. Right, a modified snake diagram of 5-HT_{2A}R. Transmembrane helices are labeled by Roman numerals and regions with significant (CL> 95%) electron withdrawing R group scores are shaded black. Residues shaded grey include those which interact with LSD in transmembrane helix III (black box), D172 and R173 (black star), and S421 (bottom; depicted as phosphorylated). The propagation of electron density between the backbone of transmembrane helix III and intracellular loop 2 is represented by black arrows. These arrows are not intended to imply that inductive effects are mediated through space, and inductive effects of this kind are, when suspected, not able to be screened by molar concentrations of sodium chloride (Ling, 1984). The snake diagram was made in GPCRdb

(Pándy-Szekeres et al., 2017) and, for artistic purposes, only a negative pole is depicted near the C-terminus. The phosphate group that would be associated with S188 is not shown.

To identify electron withdrawing sequences of interest, we employed the significance test of Karlin & Altschul (1990) for the assessment of general amino acid scoring schemes. The relevant calculations are explained in the supplementary information, and the significant (CL ≥ 95%) sequences identified are listed in Table S3. Importantly, the primary sequence analysis proposed by Ling (1984) was not statistical but rather, a calculation of the inductive index for the entire sequence that is in proximity to functional groups of interest. For our purposes, it is the similarities or differences between the high affinity LSD receptors–and high scoring regions for which the withdrawing/donating effects may not need carefully balanced–that appear most appropriate.

Sequences by which 5-HT_{2A}R could mediate a relatively unique inductive effect are found among the N-terminus, intracellular loop 2, and the C-terminus (Figure 12). Notably, these regions are poorly conserved among the serotonin receptor subfamily (Dezi, 2007), and the N- and C-termini are usually truncated for crystallography (Wacker et al., 2013; Kim et al., 2020). For LSD to exert an electronic influence in tandem with intracellular loop 2, the effect would need to propagate to and from LSD contacts in transmembrane helix III–and especially, the salt linkage between D155 and the basic nitrogen of LSD's ergoline system–through roughly 25 amino acids. More realistically, such an effect may only need to propagate to D172 or R173 of the conserved E/DRY motif. These residues are either observed (for review: Kim et al., 2020) or predicted (Perez-Aguilar et al., 2014) to undergo large rearrangements that are important for polar contacts in active-state GPCRs. Generally, the initiation of these rearrangements, and their place in the overall activation mechanism for 5-HT_{2A}R, is understudied (Kim et al., 2020). The proposed influence would need to "reach" for 8 amino acids on the C-terminal side and 17 amino acids on

the N-terminal side (Figure 12), and the feasibility of this propagation could be determined by the observation of pK_a changes, variable fluorescence lifetimes of Y174, or variable LSD fluorescence, in truncated peptides. At present, and to the best of our knowledge, a propagation of six to nine amino acids is the longest observed inductive effect in peptides (Ling, 1964; Manning & Manning, 2018).

For the N- and C-termini, the effect would need to be transmitted further or via next-neighbor interaction energies of adsorbed species such as water. While this may seem implausible, we note that synchronous, long-distance changes to the relaxation of cell water–and coupled to membrane-associated waters–is essential to the framework above (Thoke et al., 2015; Bagatolli, Stock, & Olsen, 2019). It seems important that LSD–at the nanoscale–can introduce coherent changes to brain regions that are orders of magnitude larger. Therefore, if all changes introduced by LSD to 5-HT_{2A}R are close contact, the question of a puzzling, long-range interaction is not removed but merely pushed further up the chain of interactions.

More broadly, significant scores for not only 5-HT_{2A}R, but also for 5-HT_{2B}R and D2, were found among the C-terminal portion of intracellular loop 2 (Table S3). Generally, the proportion of withdrawing R groups in this region was unusual for the receptors studied (Table S4), and intracellular loop 2 is noted for its involvement with functionally active constructs of D2 (Perez-Aguilar et al., 2014). In the cellular environment, intracellular loop 2 exists at the interface between the cytoplasm and residues that fold to form transmembrane helices III and IV (Figure 12). Along with helix VII, helix III mediates β-arrestin signaling (Wacker et al., 2013), and the coupling between LSD binding and the intracellular domain remains unclear (Chen & Tesmer, 2018). For 5-HT_{2A}R, the significant sequence identified includes H183 and R185, which are also predicted (or observed) to undergo large rearrangements in the active-state conformation (Perez-Aguilar et al., 2014; Kim et al., 2020).

Furthermore, phosphorylation of S188 and S421 are important for agonist-mediated desensitization of 5-HT_{2A}R (Gray, Compton-Toth, & Roth, 2003), and both were in or near the significantly positive regions of the inductive index (Figure 12). By the model proposed, phosphorylation of 5-HT_{2A}R may be under the influence of a relatively long-range inductive effect or, in the language above, phosphoryl groups are an "adsorbent" for which the next-neighbor energies in Equation 2 are altered significantly by LSD, and in turn may alter the next-neighbor energies for relatively distant amino acids (Manning & Manning, 2018). Notably, this proposal does not conflict with the "accessibility" to phosphorylation featured in current biochemistry (Perez-Aguilar et al., 2014), and inductive effects are coupled to steric effects (Ling, 1981). For this reason, site-directed mutagenesis to alanine–though implying a rather large change in inductive propensity–may be an ineffective strategy for the further exploration of the mechanisms proposed. Therefore, we reemphasize the dipolar-relaxation experiment, the ion balance experiment, and the determination of ionization constants and fluorescence lifetimes in truncated peptides, mentioned above.

Although characterization of structural features important for β-arrestin signaling was a crucial advance, a unifying theme for LSD biochemistry seems absent. This is not only because of the many and ostensibly unrelated reports of LSD action (the effects of LSD upon scale independent measures, the correlation between electron orbital energies and subjective effects, and so on) but because of the question of perception. In addition to the vagueness noted above, indirect realism and its hallucinations could be made consistent, after the fact, with any change to biochemical rate processes (faster, slower, more erratic) and could have been made consistent biased and unbiased signaling, equally. Put differently, the assumption of hallucinations appears prior to the biochemical data.

In contrast, the Bergson-Gibson perceptual model is only consistent with increased rate processes of the relevant systems and, given the applicability of the association-induction hypothesis, with a relatively powerful electronic effect. Given this paper's grounding of the LSD perceptual experience, a new line can be traced from the exciting research of structural biologists to the experiential effects of LSD. In the grips of indirect realism, all future biochemical data–no matter their intricacy–will remain "related" to hallucinations.[3]

Correlated Effects to the Bergson-Gibson Model

LSD and Visual Acuity

A canonical effect of LSD is the increase in absolute visual threshold unrelated to inattention or delusion (Carlson, 1958). As mentioned, increases in visual acuity are also reported via anecdote (Hawk, 2018; ITV News, 2019). These effects are puzzling, because visual acuity is generally viewed as a function of optical mechanics, for example, increasing the lens on a telescope or adjusting for refractive error in the human eye (artificially, with glasses).

By the Bergson-Gibson perceptual model, LSD may not have a mechanical consequence but rather, this increase in visual acuity may be related to changes in temporal processing. For example, visual acuity is associated with spatial frequency, the number of alternating black and white bars in a unit length (Figure 13). Normal visual acuity therefore defines, at least partially, the spatial frequency discernible as distinct black and white bars from 20 feet away. As the

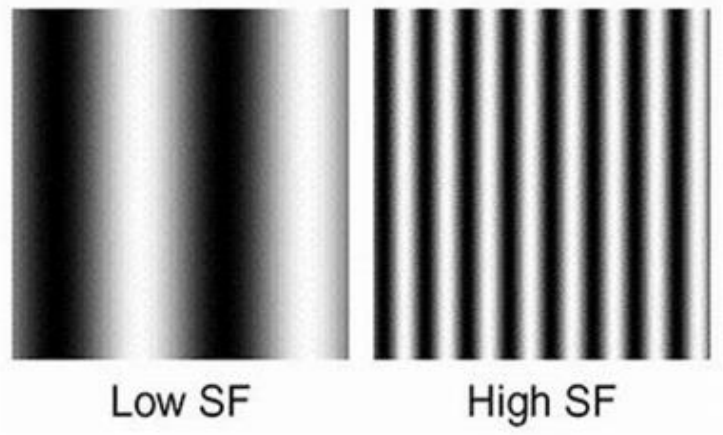
[3] The contrast between the biochemical framework above and the prevailing neurocomputational view of the action potential should be noted here. The action potential is generally viewed as a one-way chemical flow down a neuron, proceeding from neurotransmitters at the initiating dendrites, and via voltage-gated channels along the axon, to the release of neurotransmitters at the axon terminal, the strength of which is taken as a connection strength to adjacent neurons. Given multiple neurons, the matrix of connections serves as a conceptual basis for neural net computations. In the oscillatory framework proposed, the action potential is one-half of one oscillation, and a particular neuron is one oscillator within a medium containing billions of oscillators, of which the rate of oscillation is affected by electronic induction.

distance from the viewer increases, the bars fuse to an indistinguishable grey mass (Figure 13).

Spatial frequency can be transformed into temporal frequency because the high spatial frequency pattern (Figure 13, right) can be viewed as a set of waves, a black and white bar pair equal to one wave of length λ, passing right to left under a viewing window at velocity v = λf. As this velocity increases, at some point the waves again fuse to an indistinguishable grey mass.

Figure 13

Two Spatial Frequencies



Note. Left, a low spatial frequency (SF) pattern. Right, a high spatial frequency pattern.

The velocity at which this fusion occurs must be related to the highly studied rate of critical flicker fusion (CFF) at which no flicker can be seen (Birren, 1976). It is known that CFF decreases with age, particularly in "masking" experiments during which a target letter is presented, such as an 'A', followed shortly by a masking pattern superposed over the letter (Birren, 1976). With aging, in order to discern the letter, the interstimulus time that is required between the letter and the mask grows longer and may be associated with a decreased metabolic rate among older populations (Birren, 1976). Assuming all mechanical bases are equal, visual acuity A_v must be some function of our normal CFF and its velocity V_{CFF}:

$$A_v = BV_{CFF} \quad (6)$$

Here *B* is some constant. In the context of Equation 6, a higher V_{CFF} (meaning a higher CFF) would mean a higher velocity for the black and white bars passing beneath the view-window before fusing to an indistinguishable mass (Figure 13), or rather, an increase in visual acuity because A_v is proportional to V_{CFF}. This may be relevant to the examples of the foregoing: the wings of a fly flapping like those of a heron, the slowed blades of the fan, and the fuzzy cylinder moving backward through 4N-fold symmetry to a definite cube.

Therefore visual acuity, in addition to its mechanical bases, would also be a function of the timescale at which the perception-action system is set, and the latter is a function of the underlying process velocity or, in the biochemical language above, the differential adsorption dynamics.

Colors, Language, Perception and Time

Another canonical effect of LSD is the perception of color as more “vibrant” (Hartman & Hollister, 1963; Goldman, Galarneua, & Friedman, 2007). Notably, a field of color is no different a vibratory phenomenon than those mentioned previously (such as, the beating wings of a fly). Bergson (1896/1912) noted that 400 trillion oscillations of an electromagnetic field comprise one second of red light and that, if spread out such that our perception could discriminate these oscillations, many thousands of years would be necessary to count them all. By this perspective, LSD may be moving perception at the normal timescale closer to the individual vibrations of the field of color. Therefore, colors would become more vibrant under the influence of LSD and, to belabor the point, by this reasoning such vibrancy would not be a hallucination.

Similar changes to the auditory sphere are expected, such as the notes of a musical piece seeming more spread in time, and it is known that verbation become less comprehensible under

the influence of LSD (Honigfeld, 1965). For example, as each word of the sentence "the…woman…paddled…the…canoe" is spread from the others in time, a symmetric effect may occur by which memory can flood into the matrix of words. The experiences of past canoe trips–huge waves on the lake, a big walleye, the fluting loons, the boggy portages–can rush into consciousness, and the sentence may seem to resonate with inexhaustible meaning. This flooding of the internal world of memories, of thoughts, and the loosening of the normally close tie of perception to action in the present, is the entrée to what seems the hallucinatory world of LSD and may lead to the vision of a "flood of information" (Winkelman, 2017) or "overload" (Preller et al., 2019).

Virtual Action and the Scales of Time

Visual areas of the brain (V1-V4) feedforward to the motor areas and in turn, the motor areas feedback, modulating the initial information processing. This re-entrant feedback is an example of the resonance Gibson visualized, and there is an implication: in Bergson's (1896/1912) succinct phrase, perception is "virtual action". Bergson said this in the context of his holographic development wherein he visualized the universal field as a vast sea of motions or "real actions", all forming a vast interference pattern. Any given object acts upon all other objects in the field and is in turn acted upon by all other objects. It is in fact obliged:

> …to transmit the whole of what it receives, to oppose every action with an equal and contrary reaction, to be, in short, merely the road by which pass, in every direction the modifications, or what can be termed real actions propagated throughout the immensity of the entire universe. (Bergson, 1896/1912, p. 38)

To Bergson, from this vast information in the external field the body selects only the subset of real actions related to its action capabilities. What is specified and selected from the real actions are now virtual actions–how the body can act, and these are highly correlated to the

"affordances" of Gibson (1966, 1979). For Bergson (1896/1912), speaking of organisms as centers of action in this field: "…the real action passes through, the virtual action remains" (pp. 31-32).

From our discussion of LSD and of perceptual time scales surfaces a conjecture, in fact, a logical entailment of the principle of perception as virtual action. Virtual action is the very definition of veridical perception; it implies that what is being specified–the "buzzing" fly, the slowly rotating cube–is a veridical indication of actions available, e.g., to reach out and grasp the cube between thumb and forefinger placed on each of the cube's opposite sides. But introduce a powerful catalyst or inductive agent into the perception-action system such that the fly is now barely moving its wings. To remain veridical, the perception must indeed be displaying a real possibility of available actions, e.g., reaching out and grasping the fly precisely by one of its wings. If this were not the case, perception is subject to anomalies–we reach out, the fly is long gone.

Given the invariance laws underlying this specification of a fly (in the perceptual spacetime partition), nature seems to allow for such variation, and the question of whether such a hypothesis can be tested as an effect of LSD remains. Again, there will be the problem of dose: with too high a dose, the subject may not be able to process the instruction "grab...the...fly". In a microdose situation, during which the subject may indeed process the instruction, the LSD perceptual effect would be more subtle than the perception of a fly as a heron, and experimental designs would need adjusted to the specified timescale.

It may be presumed that LSD is affecting–coherently and uniformly–an integral system involving the perceptual motor areas of the brain as well as the muscular systems and their actions. An interesting and perhaps relevant example is that of baseball player Dock Ellis who pitched a "no-hitter" under the influence of LSD (Vaccaro, 2020). Holistic perspectives of LSD

action that integrate the musculature with the experiential effects have been proposed (Roddy, 2013).

The Flood of Information and the Virtual

In an excellent review, Swanson (2018) traced the influence of the "filtration theory" concerning the experiential effects of psychedelic drugs. Via filtration theory, the brain is a "reducing valve" (Huxley, 1953, cited in Swanson 2018) that normally allows into consciousness only a small portion of the internal world–an amount just necessary for those actions relevant to the extant circumstances. As these ties between the internal world and the action system are "loosened" (Swanson, 2018), a valve is opened, and information floods into inner experience. The filtration concept was tied to Osmond (1957), an early theorist who coined the term "psychedelic" and who corresponded with Huxley, the author of the "reducing valve" theory (Huxley, 1999, as cited in Swanson, 2018). Though Huxley attributed the basis of these concepts to Bergson, the work of James (1890) and Broad (1923), among others, also fit into this framework (Swanson, 2018). However, the meaning of the filtration theory is presented as incongruous:

> Osmond and Huxley argued that filtration theory concepts were fully consistent with the subjective phenomenology, psychotomimetic capability, and therapeutic efficacy of psychedelic drugs. However, it remains unclear exactly *what it is* that the brain is filtering and consequently *what it is* that emerges when the filter is pharmacologically perturbed by a psychedelic drug.
>
> Huxley (and Bergson) spoke of the brain as a device that filters the *world* and when the filter is removed we experience 'more' of reality. Osmond's 'mind-manifesting' (*psyche*) (*delic*) name, by contrast, suggests that these drugs permit latent aspects of *mind* to rise into conscious awareness. So which is it? Do psychedelic drugs manifest latent aspects of *mind* or of *world*? How we answer this question will crucially determine our

> ontological and epistemological conclusions regarding the nature of psychedelic experience. (Swanson, 2018, p. 9)

This apparent incongruity is alleviated by a deeper understanding of Bergson's prescient model. The first implication of the temporal metaphysic of Bergson is that the flow of time is indivisible and is intrinsic to the transformation of the holographic field without resort to any yet to be coherently explicated short term memory mechanism (cf. Robbins, 2017, 2020). This is what accounts for the specification of the moving fly as a continuity, as a vast set of past motions within the ever-transforming external field (at a scale of time). The second implication of Bergson's holographic reconstructive wave model of perception is that experience is not occurring solely within the brain. These two implications combined mean that being itself must be four-dimensional, with a vast dynamic time extent–or, in Bergson's terms, the dynamic time-extent is "the virtual" (1896/1912).

These aspects of Bergson's work are the essential core of the filtration model, which conceptualizes the brain as a transforming portion of the indivisibly transforming field. Though cross-sections of this transformation may be called "the present," they are equally termed "matter" (Bergson, 1896/1912), and the previous instant is deemed the past or rather, non-existence and no longer matter. The brain is matter and, because it is always present, is generally thought to be tasked with preserving and storing these instants of the past. Ignoring the difficulties for this concept of "storing" (Unger, 1973; Robbins, 2020), at minimum the brain is a cross-section of an ever-growing four-dimensional being or rather, the brain/body is the leading edge of the virtual. And this transforming brain–a perceptual apparatus oriented to possible action, as well as a reconstructive wave specifying the external environment related to action–resonates, with a structured wave pattern, to similar aspects and experiences of the virtual past. It is this resonance that both limits the entrée of the virtual into consciousness and selects those

aspects that get through even when this seems illusory. For example, a bear seen clearly in the woods may upon closer approach be only a tree stump. But equally–and with clear ecological purpose–an orange patch in the bushes that appears to be a tiger may in fact be a tiger.

Already the symmetric component of this model can be seen: the entrée of the virtual into our normal experience or perception. If there were a change to the normally precise and complex connections of the brain explored by Preller et al. (2019), then the virtual–that which is oriented normally to the present environment–becomes increasingly less so, and the apparent arbitrariness becomes greater.

Returning to language perception and the example sentence "the…woman…paddled…the…canoe", Bergson argued that the whole of the virtual, the entirety of our experience, and indeed the whole of being is behind linguistic comprehension (Bergson 1896/1912). When the words of this sentence are spread in time, the vastness of canoeing experience can pour into consciousness; the precision and abstraction of the concepts can become rich; and each word/concept can be defined as invariant over an abundance of experience. Again, a young woman who ingested 600 mcg LSD for a period of months expressed:

> Usually, we process concepts with a near direct one-to-one correspondence to words. There is a concept, and there is a word that maps onto the concept. Normally the mapping is so tight that we sometimes end up feeling like the words are the concepts themselves. This is probably why rhetoric is so powerful.
>
> On acid, this correspondence is reduced. Concepts occur wordlessly; they are experienced, like a tactile sensation in the brain...the words for the concepts are reduced to seem a bit 'empty'. (Aella, 2017)

Bergson devoted nearly two of the four chapters in *Matter and Memory* (1896/1912) to language comprehension, to speech perception, and to related linguistic aphasias. He related

these to the role of the virtual in comprehension and, by way of this, described a motor theory of speech perception–a theory later developed in detail by Liberman et al. (1967)–that is still one of the three main theories of speech perception today (Bergson's precedent largely unknown). While Bergson's general model of language comprehension is beyond scope of this paper, it serves an idea of the complexity of interactions between virtual being and the various brain regions that concern the processing of language for meaning.

This explication of Swanson's (2018) either/or question–"latent aspects of mind or of world"–is here oriented to the "aspects of mind" answer, and to an essential operation of LSD beside its perceptual timescale changes: the symmetric opening to the virtual. However, this framework of Bergson also allows for the "of world" answer, and this answer may depend upon the psychedelic drug ingested and the peculiar biochemistry thereof. Given that the brain as Bergson sees it is a selection from the universal field–and a specifying device within its vast sea of "real actions" (Bergson, 1896/1912)–the interesting question of whether the selection itself can be changed by a substance such as dimethyltryptamine, with its substantially unusual effects (Strassman, 2001), should be left open.

Conclusion

In this treatment of LSD, we have stayed with perception, and with the concept that perceptual changes are timescale changes, and at least up to a certain dose are veridical. But this narrow focus is based upon something very broad: namely, that the "all is hallucination" concept (with its implicit model of the brain and its reliance on indirect perception) may be very misguided, and may need to be replaced by a very different model of brain and mind.

This Bergson-Gibson model of the brain as a reconstructive wave specific to an aspect of the surrounding field is an intrinsically concrete treatment of the brain as a device. If considered a "resonance model of consciousness" (Peat, 1975), this resonance should be conceived as

concrete as an AC motor that generates a field of electrical force. Integrated Information Theory cannot be emended to support this, nor can Predictive Processing, nor can they incorporate the invariance laws of Gibson (1966, 1979). Abstractly equating resonance with the activations and firings of the "connectome" hypothesized by Atasoy et al. (2017) may be useful, but must ultimately be related to molecular mechanisms and concrete chemical dynamics. By way of analogy, an abstract dynamical description of the AC motor, including chaotic attractors, must ultimately become various metals, physical interactions, and classical forces. The resonant wave created by the brain, modulated by the invariance structure that defines external events, must incorporate and reflect a dynamic event structure, i.e., it must incorporate something like "computations" (Robbins, 2002) on the conventional cognitive theory.

This degree of theoretical concreteness–a theoretical vision of the brain as a concrete device–is required in order to formulate a theory of consciousness, in order to address the hard problem, and in order to understand the origin of the image of the external world. Philosophers of consciousness are coming to the realization that the abstract symbol manipulation of computers or neural nets cannot account for the emergence of consciousness or conscious perception. So, how do concrete biological dynamics solve the problem? Or rather, what do concrete biological dynamics provide–over and above symbol manipulations–that make all the difference? This paper's concrete biochemical framework, built on the theoretical foundations of Bergson's concrete fields and Gibson's concrete resonances, may provide some answers.

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Supplementary Information

LSD and Perception: the Bergson-Gibson Model for Direct Perception and its Biochemical Framework

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The inductive index was introduced by Chiang & Tai as a general, *ab initio* method for the quantification of inductive effects (1963). For the algorithm most relevant to this paper, readers are encouraged to see the method of Lara-Popoca et al. (2020). Briefly, the inductive index depends (in part) upon the sum of discrete electronegativities weighted to a single bond, and is therefore is inapplicable to resonant moieties and is difficult to calculate for the R group of proline, given its cyclic structure (Lara-Popoca et al., 2020). Values for the R groups of tryptophan, histidine, phenylalanine, and tyrosine can in theory be extrapolated from their respective alpha amino pK_a, given the caveat of variability among these data (Lara-Popoca et al., 2020). For proline, the interpolation is more difficult, as the pK_a values for its ionizable groups are disproportional (Lara-Popoca et al., 2020).

Given our purposes, we utilized pK_a values from the CRC Handbook of Chemistry and Physics (2016) because of their correlation (R^2 = .9552) to the 15 inductive index values determined by Lara-Popaca et al. (2020). By analyzing positive scores only, our interpretation mostly avoided any proposal of a specific contribution from proline (except for P180 or less importantly, P415 of 5-HT_{2A}R). We also relied heavily upon the amino acid probabilities reported by Shen et al. (2006) for the assumption that electron withdrawing regions were of interest.

That said, for the analysis of high scoring segments, the capacity of proline to donate electron density was important for the distribution. Regarding the significant regions listed in Table S3, these were insignificant (CL<.95) when the R group of proline was assigned a neutral (scaled value of 0) or weakly donating (scaled value of -1) inductive index. However, we do not find our assignment of a strongly negative value to proline extreme; proline is the only standard amino acid for which the R group is connected to the protein backbone twice. The R group of valine, for example, has a relatively high electron donating character, with a single bound carbon, and yet isopropyl groups impart the weakest inductive effect among the one- to three-carbon substituents (Pale & Vogel, 2005). It seems reasonable that proline's two, directly bound carbons would have a stronger inductive effect upon protein backbones when compared to valine or to alanine, consistent with the high pK_a of its secondary amine. Regarding the disproportionality between proline's ionization constants, at least for polypeptide backbones–for which there is only one carboxy acid–the analysis of inductive effects on distant amide linkages would need to

be calculated exactly, as suggested by Ling (1984) or as performed by Lara-Popoca et al. for tetrapeptides (2020). Because we looked for only high-scoring, positive segments, extrapolation from the pK_a of proline's secondary amine appeared more sensible than a novel calculation. However, calculations like these should remain an important goal for the inductive index.

On the other hand, Dwyer (2005), using a Mulliken population analysis for the H atom of hydroxyl moeities in substituted cyclohexanols, calculated the R group of proline to exert zero inductive effect relative to the other standard amino acids. The inductive index in Table S1 does not correlate (R^2=.099) to Dwyer's calculations that were scaled to glycine or rather, and more specifically, reflected no inductive effect of proline relative to glycine (2005). Given the value for glycine's proton in Table S1, this would imply a weakly donating effect for proline. In Dwyer's analysis, the alpha amino pK_a was a function of several electronic factors, not simply induction (2005), and for this reason, Dwyer's score for inductive effects did not correlate (R^2 = .097) to the pK_a data of Edsell (1965), whereas the inductive index in Table S1 correlates strongly to Edsell's data (R^2 = .958). Extrapolation from Edsell's alpha amino pK_a (= 10.6) to the inductive index of proline would also imply an extremely negative value. In general, we consider Dwyer's analysis extremely valuable, particularly his focus on field and resonance effects, and his proposals concerning the relation between electronic qualities and protein structure that have been long overlooked. However, we also believe his results are not in conflict with the inductive index, and it is important to reemphasize that the inductive index of Lara-Popoca et al. (2020) was correlated to tryptophan fluorescence lifetimes–a chemical property that is wholly separate from ionization constants.

Table S1

The Inductive Index

R Group	Inductive Index	Inductive Effect	Scaled Value	Probability
	From Lara-Popoca et al. (2020)			
Cys	-339.6	Donating	-8	.0231
Asp	-162.5	Donating	-4	.0484
Ala	-134.0	Donating	-3	.0704
Val	-127.1	Donating	-3	.0613

Ile	-96.8	Donating	-2	.045
Glu	-91.3	Donating	-2	.0692
Leu	-72.8	Donating	-2	.0984
Gly	-53.2	Donating	-1	.0675
Met	19.7	Withdrawing	0	.0237
Arg	46.5	Withdrawing	1	.0552
Lys	62.8	Withdrawing	2	.0565
Ser	81.5	Withdrawing	2	.0799
Gln	89.3	Withdrawing	2	.0465
Thr	92.3	Withdrawing	2	.0534
Asn	180.8	Withdrawing	4	.0368
	From this paper			
Pro	-402.4	Donating	-10	.061
Trp	-24.9	Donating	-1	.0121
His	58.6	Withdrawing	1	.0256
Phe	58.6	Withdrawing	1	.0378
Tyr	75.3	Withdrawing	2	.0282

Note. The inductive index shown, and to which we refer in the paper, is 1000 times its calculated value (Lara-Popoca et al. 2020). The five values attributed to "this paper" were extrapolated from the regression line between the alpha amino pK_a reported in the CRC Handbook of Chemistry and Physics (2016) and the 15 inductive index values determined by Lara-Popoca et al. (2020). The "inductive effect" refers to the effect on the electron density at carbon alpha. The "scaled value" refers to the scaling of proline to a value of -10, and the rest to the nearest whole number. The rightmost column refers to the probability of occurrence for each amino acid in the Human Genebank (Shen et al., 2006; NCBI Build Number 34, March 2004). The Human Genebank values were chosen because they are relatively unbiased by researchers (Shen et al., 2006).

Table S2

High Affinity LSD Receptors

Protein Name (UniProt)	Name in Text	Uniprot Accession	npK_i (LSD)
5-hydroxytryptamine receptor 1B	5-HT_{1B}R	P28222	4
5-hydroxytryptamine receptor 7	5-HT7R	P34969	3.77
5-hydroxytryptamine receptor 6	5-HT6R	P50406	3.75
5-hydroxytryptamine receptor 1A	5-HT_{1A}R	P08908	3.73
5-hydroxytryptamine receptor 1D	5-HT_{1D}R	P28221	3.7
5-hydroxytryptamine receptor 5A	5-HT_{5A}R	P47898	3.64
Dopamine D3 receptor	D3	P35462	3.16
5-hydroxytryptamine receptor 2C	5-HT_{2C}R	P28335	3.11
Alpha-2A adrenergic receptor	Alpha-2AR	P08913	2.93
5-hydroxytryptamine receptor 1E	5-HT_{1E}R	P28566	2.62
D(4) dopamine receptor	D4	P21917	2.39
D(2) dopamine receptor	D2	P14416	2.55
D(1A) dopamine receptor	D1	P21728	2.34
D(1B) dopamine receptor	D5	P21918	2.05
5-hydroxytryptamine receptor 2B	5-HT_{2B}R	P41595	3.11
5-hydroxytryptamine receptor 2A	5-HT_{2A}R	P28223	3.54

Note. The normalized K_i (npK_i) refers to the log-fold-change in affinity for LSD relative to the highest affinity receptor (Ray, 2010). Only the primary sequences of LSD receptors with npK_i > 2, defined as "perceptible" (Ray, 2010), were studied in this paper.

Theory of Calculation for Significant Regions

The scaled value in Table S1 meets both criteria of Karlin & Altschul (1990) for employment of their statistical test, that 1) the expected value is negative and that 2) at least one score is positive. Briefly, provided an alphabet of letters $A = \{a_1, a_2, \ldots, a_r\}$, a random sequence sampled independently from *A,* and

with corresponding probabilities *{p_1, p_2, …, p_r}*, and accompanying each letter a_i a score S_i, will have some maximal segment score *M(n)* for a sequence of length *n*. *M(n)* has the approximating, right skewed distribution (Karlin & Altschul, 1990):

- $$Prob\left\{\bar{\mathrm{M}}(\mathrm{n}) > x\right\} \approx 1 - \exp\left\{-\mathrm{K} * e^{-\lambda * \mathrm{x}}\right\} \quad \text{(S1)}$$

Here λ^* is the unique positive solution to the equation (Karlin & Altschul, 1990):

$$\sum_{i=1}^{r} p_i \exp\left\{\lambda s_i\right\} = 1 \quad \text{(S2)}$$

And *K** may be approximated by (Karlin & Altschul, 1990):

$$K^* = C^* \left(\frac{\lambda^* \delta}{1 - \exp(-\lambda^* \delta)} \right) \quad \text{(S3)}$$

Here δ is the smallest span of scores. When all scores are integers and have a greatest common divisor of 1, then $\delta = 1$ (Karlin & Altschul, 1990), and this simplification was a motivation for scaling the inductive index. The value *C** is calculated by (Karlin & Altschul, 1990):

$$C^* = \frac{\exp\left\{-2\sum_{k=1}^{\infty} \frac{1}{k} (E[e^{\lambda^* S_k}; S_k < 0] + p(S_k \geq 0))\right\}}{\lambda^* E[S_1 e^{\lambda^* S_1}]} \quad \text{(S4)}$$

Here $E(S_k)$ is the expected value of the score *S* of *k* independently chosen values, and the exponent of the numerator converges geometrically. Given the scaled inductive index, and the

probabilities listed in Table S1, Equation S2 can be expanded and λ^* can be found equal to .26097. K^* is equal to .40036. For a given confidence level, say 95%, a critical value x must be obtained by (Karlin and Altschul, 1990):

$$\exp(-e^{-\lambda^* x}) = .95 \tag{S5}$$

Solving for x in Equation S5 gives the following relationship between a score S, that is significant at the 95% level, and the other constants and variables listed above (Karlin & Altschul, 1990):

$$S > \frac{(\ln n + \ln K^*)}{\lambda^*} + x \tag{S6}$$

For n, 10 amino acids or less provide a useful estimate, because the propagation of inductive effects across six to nine amino acids is, to the best of our knowledge, the longest transmission observed (Ling 1984; Manning & Manning, 2018). We should make clear, in Manning & Manning (2018) it remains an open question whether this effect is mediated through the polypeptide backbone or through space. Both could have interesting implications for the inductive index. Furthermore, as mentioned in the text, several experiments performed by Ling (1984), by Thoke et al. (2018), and by Begarani et al. (2019) imply a much longer transmission of the inductive effect than 10 amino acids. It is important to remember, in the example of ouabain from the paper, “1000 amino acids” does not mean “a single inductive effect that spans 1000 amino acids in the absence of any intervention.” Rather, by way of the next-neighbor effect, the entire transmission is thought to propagate by way of only a few amino acids at a time (Ling, 1984). In theory only, the feasibility of these effects turns crucially on the assignment of a “transmissivity factor” in the calculation of the inductive index, that was not discussed in our paper and that is presumed to be

dramatically altered by the resonant peptide backbone (Ling, 1984). For more information, readers are encouraged to see the interesting discussion of the transmissivity factor in Ling (1984) and in Lara-Popoca et al. (2020).

Last, the Karlin and Altschul analysis is weighted against very short sequences (it is too hard for them to be significant). Many sequences, such as 217RRRRKR222 of the dopamine D2 receptor, which is composed entirely of electron withdrawing R groups, and is important for the formation of noncovalent interactions between D2 and 5-HT_{2A}R (Lukasiewicz et al., 2010), were not significant to our analysis but are of the type of region for which Ling thought inductive effects were highly relevant.

Importantly, the inductive index was applied to primary sequences and so, disulfide bonds, other important modifications, and solvent effects were not considered in our study. These are presumably a future direction for the inductive index (Lara-Popoca et al., 2020). Our primary sequence analysis was performed in Excel, Desmos (2020), and OmniCalculator (Díez & Szczepanek 2020). Full calculations and the spreadsheet of primary sequences will be made available by the authors, without undue reservation, to any researcher.

Table S3.

Significantly Positive Regions of the Inductive Index among 16 High-affinity LSD Receptors

Protein	Position	Sequence	CL
5-HT_{5A}R	328-334	YSNSFFN	.95
5-HT_{5A}R	338-347	YTAFNKNYNS	.97
5-HT_{5A}R	341-350	FNKNYNSAFK	.97
5-HT_{5A}R	342-351	NKNYNSAFKN	.98
5-HT_{5A}R	343-352	KNYNSAFKNF	.97
5-HT_{5A}R	344-353	NYNSAFKNFF	.96
5-HT_{1E}R	223-232	SNRSTDSQNS	.95
D2	142-151	YNTRYSSKRR	.97
5-HT_{2B}R	164-169	NQYNSR	.95
5-HT_{2A}R	8-17	NTSLSSTTNS	.97

5-HT_{2A}R	182-191	HHSRFNSRTK	.95
5-HT_{2A}R	425-434	QMGQKKNSKQ	.95

Note. Because the sequences listed above were (in some cases) made up of smaller significant sequences, here we report only the longest sequences that did not overlap entirely. In Table 1 of the text, "significant regions" refers to significant regions that did not overlap at all. Remarkably, for 5-HT_{5A}R, a region of several significant and coextensive positive sequences was found at the C-terminus. By the framework proposed in the text, this region may be relevant to the mediation of behavioral effects attributed recently to this protein (Popik et al., 2019).

Table S4.

Electron Withdrawing Character of Intracellular Loop 2 Among High Affinity LSD Receptors

Protein	IL2 (UniProt)	C-terminal portion
5-HT_{1B}R	146-165	E**YS**A**KRT**P**KR**
5-HT7R	179-201	V**RQN**G**K**C**M**A**K**
5-HT6R	123-144	**K**L**RMT**PL**R**AL
5-HT_{1A}R	133-152	D**Y**V**NKRT**P**RR**
5-HT_{1D}R	135-154	E**YSKRRT**AG**H**
5-HT_{5A}R	138-158	**YT**L**RTRK**CV**S**
D3	127-149	**H**G**T**G**QSS**C**RR**
5-HT_{2C}R	151-170	E**HSRFNSRTK**
Alpha-2AR	145-166	**N**L**KRT**P**RR**I**K**
5-HT_{1E}R	119-138	E**Y**A**RKR**T**A**K**R**
D4	132-152	**YNRQ**GG**SRRQ**
D2	131-151	**YNTRYSSKRR***
D1	120-138	**FRY**E**RKMT**P**K**
D5	137-158	**KRKMTQRM**AL
5-HT_{2B}R	152-171	**Q**A**NQYNSR*A**T**
5-HT_{2A}R	172-191	**HHSRFNSRTK***

Note. In each case, the last 10 amino acids of IL2 are listed. Bold, boxed residues have "electron withdrawing" R groups according to Table S1. An asterisk represents significance (CL>.95) according to the statistical method of Karlin and Altschul (1990). For the rest, given the probability (.444) of an electron withdrawing R group in the human proteome, the decimal odds of there being less than 8 withdrawing groups among 10 randomly chosen amino acids can be calculated from Pascal's triangle to be roughly .975. Given this value, the odds that 7 out of 16 of these regions, chosen at random, would have at least 8 withdrawing groups is quite small. Against (part of) the objection that amino acid occurrence would follow conventional sequence predictions, we note that the inductive index in Table S1 is correlated to neither the genomic hydrophobicity scale (R^2=.008) nor to the transmembrane tendency scale (R^2=.002) as reported by Zhao (2006).

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