Perception is in the Details:
A Predictive Coding Account of the Psychedelic Phenomenon

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Abstract

Psychedelic substances are used for clinical applications (e.g., for treatment of addictions, OCD, anxiety and depression) as well as an investigative tool in neuroscientific research. Recently the idea that the psychedelic phenomenon stems from the brain reaching an increased entropic state has been put forward. In this paper, we use the predictive coding framework to formalize the idea of an entropic brain by combining notions proposed by Kwisthout & van Rooij (2015) regarding the importance of the amount of details or granularity of predictions, and Bastos et al.'s (2012) canonical microcircuits for predictive coding. We propose that the increased entropic state is created when top down predictions in affected brain areas break up and decompose into many more overly detailed predictions due to hyper activation of 5-HT_{2A} receptors in layer V -pyramidal neurons.

In the second part of the paper we demonstrate that this novel, unified theoretical account can explain the various and sometimes contradictory effects of psychedelics such as hallucination, heightened sensory input, synaesthesia, increased trait of openness, ‘ego death’, time dilation, and increased creativity and childlike cognition by up-regulation of a variety of mechanisms the brain can use to minimise prediction error under the constraint of decomposed prediction.

Keywords: predictive coding; psychedelics; level of detail; Bayesian networks, Lysergic acid diethylamide, Psilocybin.

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1. Introduction

A recent review paper (Nichols, 2016) examines both the current scientific knowledge regarding psychedelics as well as the many positive results in clinical experiments using psychedelics to treat depression and addiction. The current consensus is that psychedelics cause their effects by being agonists or partial agonists of serotonin 5-hydroxytryptamine 2A receptors, with particular importance to those expressed on apical dendrites of neocortical pyramidal cells in layer V. The 5-HT_{2A} receptors are excitatory receptor making the neurons more likely to fire. It is also known that within the neocortex, 5-HT_{2A} receptors are not distributed equally and different areas have different binding potentials. Higher binding potentials can be found in prefrontal and visual areas while the motor cortex has lower binding potentials (Forutan et. al, 2002; Ettrup et. al, 2014).

The term 'The Entropic Brain' was coined by Carhart-Harris (2014) to describe the state of the psychedelic brain, allowing the brain to be in more states than usual. This idea is based both on fMRI and Meg studies by this group. In an fMRI study following administration of Psilocybin (Carhart-Harris et al.,2014), researchers found an increase in the variance of activity within specific networks such as the default mode network, frontal parietal and salience networks. They suggested that this higher variance of activity allows for enhancement of the repertoire of possible states over time, hence an entropic brain. Muthukumaraswamy et al. (2013) performed an MEG study following administration of Psilocybin. They found desynchronization of neural activity especially in the slower alpha and beta rhythms, meaning neurons were acting in a more disjoint and separate way, suggesting that the brain was at a higher entropic state. Using dynamic causal modelling and the canonical microcircuit thought to recapitulate the intrinsic circuitry of individual cortical regions (Bastos et al., 2012) they found that the desynchronization is "likely triggered by 5-HT_{2A} receptor-mediated excitation of deep pyramidal cells" (p. 15171).

In the next section we will introduce the main ideas of the predictive coding framework focusing on ideas from Kwisthout & van Rooij (2015) regarding the importance of the amount of details or granularity of predictions as well as take a

deeper look at Bastos et al.'s (2012) canonical microcircuits for predictive coding. We will then formulize the idea of the entropic brain and by considering the specific roles suggested for alpha and beta rhythms within the predictive coding framework we will offer a testable hypothesis.

In the second part of this paper we will show how this formalisation can explain the various and sometimes contradictory effects of psychedelics.

2. Predictive Coding

In his book "The Doors of Perception" (1954), Aldous Huxley described some of his psychedelic experiences, which led him to propose the idea that perception is a door between things that are known and things that are unknown. This idea turned out prescient of the contemporary predictive coding account of brain processing. According to predictive coding, perception is a continuous process of combining the brain's previous knowledge with new incoming data The brain is thought to combine these different data streams by using Bayesian updating so as to best represent the environmental causes of its sensory input. This enables the brain to predict its future state which is an evolutionary necessity.

Furthermore, the brain is thought to create a hierarchically ordered model (Bastos et al., 2012). For any pair of levels, the higher-level will have hypotheses predicting the bottom-up signals from lower-levels. The hypothesis that generates the best predictions will determine perception. Calculating which hypothesis generates the best predictions is done by calculating the posterior probability of the hypothesis. The posterior probability combines both the likelihood, how well the hypothesis predicts the bottom up input and the prior probability of the hypothesis before receiving the input. This can be seen as an advantageous tactic especially under conditions of noisy unreliable bottom up data, since previous knowledge can be used to come up with the best hypothesis.

The predictions stemming from the best hypothesis inhibit the bottom up incoming data 'explaining it away'. Only information that has not been predicted by the best hypothesis remains as 'prediction error' and propagates to higher levels in the hierarchy. Contextual information is part of competing hypotheses. An example is Dr. Jekyll and Mr. Hyde (Kilner, Friston, & Frith, 2007) both holding a scalpel. Two

competing hypothesis are created, predicting a helpful operation or a gruesome murder. Different higher-level contextual prior probabilities about the hypothesis are used to determine the winning hypothesis. Nurses in an operating room will have a higher prior that Dr. Jekyll is performing a lifesaving operation while a crowd watching a horror movie will expect a murder by Mr. Hyde. Both nurses and a crowd in the movie will combine their prior knowledge with incoming information. For instance hearing a scary laughter in the scene will cause the nurses to be surprised while the crowd will accept it.

Recently, Kwisthout and colleagues proposed a distinction between the precision of a prediction and the amount of details or granularity of predictions (Kwisthout & van Rooij, 2015, Kwisthout et al., in press). This work has shown that more detailed predictions cause higher prediction errors. This work is based on the idea that higher cognitive functions as represented by neuronal group activity are likely to be discrete and better described by categorical (discrete) probability distributions rather than the traditional Gaussian densities (Friston et al., 2015). An important distinction between Gaussian densities and categorical probability distributions is that in the latter the state space granularity (how detailed are the generative models and the predictions that follow from them) is crucial. Whereas the amount of uncertainty (or precision) in a Gaussian density can be adequately described by its variance, a categorical distribution needs both the state space granularity and the entropy of the distribution to describe its precision (Kwisthout & van Rooij, 2015).

Bastos et al. (2012) have suggested a ‘Canonical Microcircuit’ that implements the predictive coding framework in the brain. The idea of a Canonical Microcircuit is that a cortical column contains the circuitry necessary to implements a form of Bayesian inference computation and that these circuits can be replicated with minor variations throughout the cortex. The Microcircuit model is based on evidence showing that superficial pyramidal cells have forward connections to higher areas in the brain hierarchy while deep layers, including pyramidal cells in layer V of the cortex send back propagating signals to lower areas. Bastos et al. present evidence showing that these backwards connections are inhibitory and fit the notions of top-down ‘predictions’ as suggested by the predictive coding framework, while forward connections fit signals representing ‘prediction error’.

---------- Figure 1 about here ----------

Bastos et al. (2012) further suggest that superficial layers of cortex show neuronal synchronization and spike-field coherence predominantly in the gamma frequencies, while deep layers prefer lower (alpha or beta) frequencies. In essence, claiming that the top down predictions are communicated by lower alpha or beta frequencies while prediction error is communicated by faster gamma frequencies. Additional evidence for this has been found both in the visual cortex (Bastos et al, 2015; Zheng & Colgin, 2015) and higher domains of the cortex (van Pelt, 2016). While synchronisation of post synaptic neuronal groups creating brain wave oscillations are thought to be needed for communication between brain areas and passing of information, the actual information is thought to be found in the a sparse coding of neuron spiking as very specific timings compared to the oscillations (Fries, 2015, Jensen, Gips, Bergmann, & Bonnefond, 2014). We shall discuss this further when we discuss the specifics of our theory.

In the next section we will show how combining notions from Kwisthout and van Rooij (2015) regarding the importance of the amount of details or granularity of predictions and Bastos et al.'s (2012) Canonical Microcircuits for Predictive Coding brings about a clear unified and testable theory regarding the process in which psychedelics influence the brain.

3. Model

As we have seen the effects of psychedelics stem from the 5-HT_{2A} receptors on pyramidal cells in layer V (see Figure 1) being activated, lowering the threshold of individual neuronal firing and thus desynchronizing the activity of the neuronal population. We have also seen that the information communicated by the synchronous activity of these specific cells is likely to represent the brain’s top-down predictions.

Taking into account Kwisthout & van Rooij (2015) notions of granularity and level of detail of categorical predictions, we suggest that hyper activation of the cells in layer V decompose the broad categorical prediction that is usually calculated by this neuronal population into sub categories, creating a more granular set of higher detailed predictions. These decomposed predictions stemming from prefrontal, parietal and somatosensory cortex which are sent backwards to lower layers of the

cortical hierarchy, are likely based on the subjective subcategories that compromise the broader category.

---------- Figure 2 about here ----------

The newly decomposed higher detail prediction which has the highest posterior probability now dominates perception. However, under most conditions, no matter which of the higher detailed decomposed predictions best fits the data it will still fit less data than the 'usual' broad prediction. This will cause a higher level of bottom up prediction error and as we shall see in the second part of the paper compensatory mechanisms called to deal with this higher level of prediction error explain the wide variety of psychedelic effects.

---------- Figure 3 about here ----------

This theory can be tested using Granger causality measurements of slower alpha/beta frequencies vs gamma as used to determine the flow of information in Bastos et al (2015) or van Pelt (2016). Our model claims that 5-HT_{2A} agonist cause decomposed predictions from prefrontal, parietal and somatosensory cortex weakening the effect of feedback flow of predictions to lower brain areas. Thus, we postulate that administration of 5-HT_{2A} agonist would result in a lower Granger causality measurement for slower rhythms (alpha/beta) when testing areas rich in 5-HT_{2A} receptors, for instance the prefrontal cortex, compared to lower level of the brain hierarchy, for instance V1.

We further predict that under some cases it should be possible to find an increase in the Granger causality of fast gamma rhythm stemming from lower areas of the cortex to higher areas. This will reflect the expected increase in prediction error. However, as we will see this will be dependent on incoming data and the chosen mechanism to deal with the increased prediction error. A very controllable experimental design will be needed in order to predict exactly which areas in the brain hierarchy will be affected by the increase in prediction error. Individual differences might also make this a harder measurement to find.

3.1 Model Toy example

To clarify further what a decomposed set of predictions means, imagine a person walking in the forest receiving some sensory input. Under regular conditions the set of her predictions might be (see Figure 3): Pr(Animals)=0.4, Pr(Plants)=0.6. Using information theory we can measure the relatively low entropy of these predictions, with the exact amount being $H(P) = \sum p_i \log(1/p_i) = 0.9710$ bit. This means there is relatively little uncertainty regarding these possible predictions. Now let us imagine this person has consumed some 'magic mushrooms' containing the Psilocybin. Under this condition his set of predictions will decomposed for instance: Pr(Birds)=0.2, Pr(Dogs)=0.1, Pr(Butterfly)=0.09, Pr(Elf)=0.01, Pr(Trees)=0.3, Pr(Grass)=0.6, Pr(Flowers)=0.1.

As we can see, the main categorical predictions of 'Animals' and 'Plants' break up, each into more detailed sub categories.

---------- Figure 3 about here ----------

These decomposed predictions bring about a higher entropic state, $H(P)= \sum p_i \log(1/p_i) = 2.4933$ bit. In most cases this will result in higher prediction error from lower layers as these decomposed predictions 'explain away' less of the prediction error from lower layers than normal. The 'extra' predictions being activated are likely to be dependent on a subject's personal experiences and history. In general we should expect a flattening of the prediction distribution, well established prediction categories that contain many subcategories will be effected more than predictions with fewer subcategories (see figure 2). Statistically, the more subcategories a prediction has, the more likely some of them will be activated individually due to lowering the threshold of individual neuronal firing.

3.2 The importance of bottom-up data in this process.

A known saying in the psychedelic community is "set and setting". Set represents mind set and can be compared to the brain's predictions while setting is considered the environmental data. When precise environmental data combines with decomposed higher detailed predictions the result will be a uniquely clear perception. This type of perception is commonly described by users and can be read in Aldus Huxley's description of the vividness of Red Hot Poker flowers he perceived while under the influence of psychedelics (Huxley, 1954). However, due to environmental

changes and noise this clear perception is not likely to stay stable over time. The noisier the bottom-up signal the more the top-down predictions influence perception (Seth, 2014) (Figure 4). An example of this effect can be seen in Charles Bonnet syndrome (Menon, Rahman, Menon, & Dutton, 2003). In this syndrome partial or severe blindness results in visual hallucination due to activity in mid layers (Fusiform face area) enforcing their prediction on a noisy or weak signals (Blom, 2010).

---------- Figure 4 about here ----------

Under decomposed predictions, lowering precision of sensory data can result in misclassification of the data. The best explanation for the imprecise 'noisy' data might be one of the sub-threshold predictions that got activated. This will result in a 'hallucination'.

Psychedelics are known to be unique in that they can both obscure and distort perceptual data or add clarity and give the sense of enhanced resolution. As we have explained these two different sides of the psychedelic experience are dependent on the precision of the bottom-up data. As experienced users recommend a dimly lit environment is preferable if one wishes to enhance visual hallucinations (psychedelicfrontier.com).

4. Previous research under new light

In the following section we will review previous research findings in light of our account and see how they clarify and shed further light on the results.

Kometer et al. (2006) presented Kanizsa 'triangles' to subjects after administration of psilocybin. Within the Predictive Coding framework (Pellicano & David Burr, 2013) the reason this shape is perceived as complete triangles and circles rather than the complex shapes that they actually are is because "The natural statistics of the world makes the single triangle more probable (Pellicano & David Burr, 2013)". It is a top-down learnt prediction that causes this effect. Viewing this shape under normal conditions has been shown to evoke a unique change lowering of voltage as measured on the skull 170 ms after presentation of this stimulus. This is known as the N170 ERP. Following administration of psilocybin researchers found a decrease in strength of this ERP suggesting a lowering in strength of these predictions. This is in accordance with the model of decomposed predictions, since

decomposed predictions will indeed cause each prediction to be weaker than normal. This same experiment also found desynchronization of alpha band which we have discussed previously.

In a behavioural experiment Spitzer et al., (1996) found increased indirect semantic priming after administration of Psilocybin. They claim their data suggests that Psilocybin leads to an "increased availability of remote associations and thereby may bring cognitive contents to mind that under normal circumstances remain non activated". This would indeed be expected if broad categorical 'semantic' predictions are decomposed activating many more detailed semantic predictions allowing for more remote associations to be activated. In a recent experiment (Family et al., 2016) these results have been confirmed using a picture-naming task and the psychedelic, LSD.

Howey et al., (2008) explain binocular rivalry, a phenomenon of visual perception in which perception alternates between different images presented to each eye, within the Predictive Coding framework. They claim there is a hyper prior that there can only be one object in one location in time and thus your brain will alternate between predicting one object and then another. Carter et al., (2006) found that Psilocybin increased mixed states in binocular rivalry. This can be explained by decomposition of this hyper prior so that the notion of "more than one object in one location" now becomes a possible state. We will note that this effect was seen also after pre-treatment with the selective 5-HT_{2A} antagonist Ketanserin but at different times and not as strongly.

5. Minimizing prediction error

Under normal conditions the brain can decrease prediction error in a number of different ways (Friston, 2010; Friston et al., 2012; Kwisthout, 2014). It could update predictions; update the causal model that generated the predictions; it may lower prediction error by intervening in the world, either actively acting upon it, known as active inference (Brown, Friston, & Bestmann, 2011) or passively gathering additional observations and sampling information in a different way.

In this section, we explore how upregulating these mechanisms in order to deal with the increased prediction error caused by decomposed predictions can explain many of the documented psychedelic affects.

5.1 Updating the predictions

Let us consider the example of the person walking in the forest once more. As we have explained, in the case of decomposed predictions less of sensory input will be explained by any specific prediction. This will cause higher levels of prediction error. A mechanism the brain might use to minimize prediction error is to change the prediction distribution. For instance, the prediction might change to: Pr(Birds)=0.1, Pr(Dogs)=0.2, Pr(Butterfly)=0.01 Pr(Elf)=0.09, Pr(Trees)=0.6, Pr(Grass)=0.3, Pr(Flowers)=0.1. As the predictions remain decomposed no prediction will be enough to explain away the prediction error for long and so once again the distribution will change and perhaps this time the probability of an Elf will grow even further until it becomes the leading prediction and affects perception. This constant revising of the probability distribution will lead to a destabilization of perception. Objects, scenes and even abstract thoughts will 'morph' and change at a rapid speed each of which reflecting the best possible prediction at that moment. A room might look bigger or smaller, the prediction of the light condition might change causing colors to morph, while looking at your own face you might see your most beautiful prediction and your ugliest one after each other. This is the cause of individuals reporting a tendency to see "multiple viewpoints" (Sessa, 2008).

5.1.1 Upregulating predictions from other networks. Predictions from other layers of the brain hierarchy that were not affected by activation of the 5-HT_{2A} receptors can be upregulated by either increasing their relative strength or lowering their level of detail. This will cause the predictions from these layers to enforce their predictions on more of the incoming data. An example of how this might happen can be seen in Google's computerised neural network 'deep dream' (Mordvintsev et al., 2015). This hierarchical network was originally created to identify images. By allowing different parts of the hierarchy to increase their predictions these networks were able to produce hallucinatory affects. The increase in predictions could happen at different layers of the hierarchy. Increasing lower layers networks that identify lines created images with amplified lines, while increasing predictions from higher level abstract layers such as a layer that identify building created images with 'imaginary' buildings being imposed on the original picture.

Further proof that this is happening in the brain can be seen in the work of Bressloff et al. (2001). Their work looked at the low level properties of the human visual area V1 and simulated the predictions of this network. They compared their results to geometrical hallucinations drawn by people on LSD and found remarkable resemblance. This shows that increased predictions from V1 are likely to be behind the specific geometrical visual hallucination.

Furthermore, Carhart-harris et al. (2016) found that Increased visual cortex cerebral blood flow (CBF) as well as greatly expanded primary visual cortex (V1) functional connectivity profile correlated strongly with subjects ratings of visual hallucinations. It is impossible to know at the moment whether the increase in CBF is due to increased predictions errors, upregulating of predictions or both. The increase in functional connectivity profile is in accordance with prediction error from V1 being explained by predictions from other networks which will be discussed further in the next section.

5.1.2 Using prediction from other modalities - Synesthesia. When extremely high levels of prediction error occur in the brain, predictions from networks that usually predict a specific modality might be used to explain information coming from a different modality. This is the explanation for synesthetic perception that might occur under psychedelic influence. For instance the most common experience seems to be crossing the modalities of sight and sound. Higher prediction error probably stemming from the auditory cortex connects to visual predictions from other parts of the brain and the sensation of seeing sound occurs. This is known among psychedelic users as a psychedelic soundscape.

Evidence for this process is seen in recent experiments. G. Petri et al., (2014) conducted an fMRI study following administration of psilocybin. They found that resting state functional connectivity increased throughout the brain. They conclude that "Psilocybin disrupts the normal organization of the brain with the emergence of strong, topologically long-range functional connections that are not present in a normal state." We postulate that these long range functional connections arise as a mechanism to deal with increased prediction error and represent predictions from networks that usually predict a specific modality now explaining other modalities.

5.1.3 Effects of Updating Predictions. Many other known effects of psychedelic can be explained by the mechanisms described above. For instance the

enhanced suggestibility in healthy volunteers after LSD administration (Carhart-Harris et al.,2016) can be understood as a unique form of synaesthesia similar to 'mirror touch synaesthesia' a condition which causes individuals to experience the same sensation (such as touch) that another person feels. A predictive coding model of this non-drug induced phenomenon can be found in research by Ishida, Suzuki, & Grandi, (2015). In essence predictions from networks dealing with modelling the "other" begin explaining prediction error from networks modelling the self. In this manner suggested predictions from an outside source might become 'self' predictions.

Another well documented effect is known as 'Time Dilation' in which subjective time seems to slow down. A few minutes can subjectively be perceived as taking much longer. Here we postulate that subjective sensation of time is dependent on the amount of prediction error and possibly prediction updates the brain makes in order to minimize prediction error. This idea is based on the work of Ulrich et al., (2006) who discovered that the extent to which the stimulus can be predicted affects time perception, with unexpected stimulus perceived as longer. Tse et al., (2004) found a similar result, stimulus which stands out as different from all the others in a series appears to last longer than the other stimuli. High level of prediction updates might cause the subjective feeling that more time has passed. This is similar to the first day of a trip to another country seeming longer because it is filled with so many new experiences and so many prediction updates must happen in that day.

The last phenomenon we would like to touch upon is the notion of 'Ego death' many psychedelic users report. Within the Predictive Coding framework Apps & Tsakiris, (2013) describe a theoretical account of the neural and computational basis of self-recognition. In this account one's body is processed in a Bayesian manner as the most likely to be "me". Such probabilistic representation arises through the integration of information from hierarchically organized unimodal systems in higher-level multimodal areas. As we have seen, the brain's attempt the minimize increased prediction error breaks down this hierarchical structure which might lead to a total inability to distinguish between environment and self and the unique perception of 'oneness' described by many experiencing 'ego loss'.

While Apps & Tsakiris account deal with the 'minimal self', we postulate looking at the 'higher ego' as a collection of high level relatively inflexible

predictions regarding the future behavior of the 'self-organism' in a variety of situations. Alice's ego might hold a set of predictions that includes: 'I'm afraid of heights', 'Smoking relaxes me', 'I'm smart and get good grades' and many more. Following administration of 5-HT_{2A} Agonist these categorical predictions will break up based on the subjective pieces of information compromising this category. Alice might remember the time she got a D in English and her prediction about being a good student might break down into less stable forms thus destabilizing the 'higher ego'. Combining this destabilization of ego with bottom up information coming from a therapy session and a therapist suggestions might change allow Alice to think: "I'm not afraid of heights", "Smoking is not good for me" and many other. As we shall see in the next section this might have a long term effect and explain the success of many of the clinical trials regarding psychedelic therapy in drug addiction, depression and obsessive compulsive disorder.

Lastly, as parts of Alice's brain now produce these constantly changing predictions other parts of her brain might, for perhaps the first time, perceive these 'ego' networks for what they are, a relatively arbitrary set of prediction which formed mainly due to historical reasons. While some people might find this very scary others seem to find the freedom this state incurs.

5.2 Minimizing prediction error by updating the model - long term learning effects.

Within the Predictive Coding framework the model constructed by the brain is considered to be encoded in the network connectivity. Changes in this connectivity will lead to long term learning. While learning effects in humans after administration of 5-HT_{2A} agonists have not directly been studied in the last decades an interesting study in rabbits has found that agonists at the 5-HT_{2A} receptor including LSD enhanced associative learning at doses that produce cognitive effects in humans (Harvey, 2003).

Using the Predictive Coding framework, depression, addiction and obsessive compulsive disorders have been suggested to stem from overly strong and narrow predictions from certain networks that get 'stuck' (Edwards et al., 2012) and aren't updated based on the bottom-up data. Momentarily decomposing these predictions by 5-HT_{2A} agonists, especially with a combination of supportive bottom-up information

coming from a therapeutic setting, might lead to long term model updates. This could be the reason behind the success of recent clinical trials that have used 5-HT_{2A} agonist to treat these disorders.

A long term model update that psychedelic are known to cause is increasing the trait of 'openness' (MacLean, Johnson, & Griffiths, 2011). The mechanism we suggest to explain this is as follows. A higher prediction error state caused by administration 5-HT_{2A} agonists coupled with a positive rewarding setting, leads to surprise becoming a more sort after state. Interest in exploring the unknown and trying new things might grow and people might be 'motivated to enlarge their experience into novel territory' which is what defines the trait of openness (DeYoung et al., 2009). Once more the importance of a positive environmental setting is put into light and we would postulate that this increase in openness does not occur among those who have had a 'bad' trip.

When discussing the long term effects of psychedelics it is imperative to mention also the danger of hallucinogen persisting perception disorder, HPPD in short. Halpern & Pope, (2003) sum 50 years of HPPD research saying "HPPD appears to be a genuine but uncommon disorder, sometimes persisting for months or years after hallucinogen use and causing substantial morbidity. It is reported most commonly after illicit LSD use, but less commonly with LSD administered in research or treatment settings, or with use of other types of hallucinogens." We might postulate that in some conditions the brain might update its model to represent a constant state of decomposed predictions or perhaps one of the mechanisms to minimise prediction errors described above turns into a long term model update permanently changing neuronal connectivity. This understanding might allow for new approaches in categorising and treating HPPD which is usually treated with neuroleptics, anticonvulsants, benzodiazepines, and clonidine.

5.3 Minimizing prediction error by acting on the environment

Another mechanism of minimizing prediction error is intervening in the world (i.e., acting on the environment) (Clark 2013, Brown, Friston, & Bestmann, 2011). This changes the actual inputs and sets some of the model's parameters and thus decreases uncertainty. Changing the brain's input can happen both in a passive way,

for instance by moving one's eyes, or by actively moving objects in the environment. Since 5-HT_{2A} receptors are not as prevalent in the primary motor cortex, top-down prediction from that area wouldn't be as affected and this mechanism is likely to remain intact even under the influence of Psychedelics. This can explain why hallucinations seem to grow stronger while sitting still and can help influence harm reduction policies. By creating motor output, for instance while walking or dancing the mechanism of active inference (Brown, Friston, & Bestmann, 2011) in which motor output minimises proprioceptive prediction error between the expected and actual position of one's limb, bringing the actual position closer to the expected position, might enable the brain to lower prediction errors stemming from other parts of the brain too.

5.4 Changing weight of prediction error – building up tolerance

While chemical tolerance to Psychedelics drugs should not exist more than a few days after ingestion (Leshner, 2001) many experienced users will admit that the first few experiences feel stronger than later experiences and increased dosage is needed to reach the same state. This might happen as a result of the brain's attempt to minimize prediction error by lowering the weight of the prediction error or attributing this higher prediction error to 'inherent' noise that does not need to be explained. An example of inherent noise that the brain learns to ignore can be seen in a fair coin toss (Kwisthout et al., accepted). Even if you guess the coin will land on 'heads' and then it actually lands on 'tails' no surprise will follow. The brain has learnt that this type of stochastic noise is inherent to a fair coin toss. The same could happen under extended use of psychedelics. The brain could learn that this state is inherently noisier and lower the weight of the prediction error. We can only postulate that this might happen through affecting the dopamine system which has been implicated in precision weighting of prediction error (Friston et al., 2012).

5. Creativity and Childlike cognition

The idea of Psychedelics reverting the brain to an earlier developmental stage has been put forward by developmental psychologist Alison Gopnick in her book The Gardener and the Carpenter (2016). This seems to fit well with our model as research has shown that children's categorical predictions are indeed more decomposed and

detailed. For instance infants can differentiate Chinese tones as well as English (Kuhl et al., 2005) an ability that is lost to adults as their predictions clump together in wider categories based on the environment they grow up in. The same thing happens with differentiation between inserting close fit objects to loose fit objects into a container (Hespos & Spelke, 2005). Infants will perceive these actions differently while adults will group these actions into a single category, unless they are Korean and have a different word to describe these actions. Infants are not born with most of the predictions needed to navigate the world successfully and the way to learn correct predictions seems to first go through a stage of a larger granular set of higher detailed predictions which slowly come together and generalize into wider categorical predictions based on environmental and social feedback. Gopnick further states that younger learners are better than older ones at figuring out unlikely options. And that when children make mistakes it is often because they are looking too hard for essences even if there is none. As we have shown both these statements are relevant to the psychedelic phenomenon and can be explained by the combination of decomposed top down predictions and the different types on the bottom up information flow. Precise bottom up information combined with decomposed predictions can lead to hyper accurate models while imprecise bottom up data can lead to hallucinations.

Decomposed predictions might also be seen as a basic mechanism of creativity which is also postulated to be increased in children. In a famous experiment Harman et al. (1966) gave a dose mescaline to well-known scientists that were stuck on a problem. Many of the scientists that participated reported a breakthrough due to this session.

Taking our theory into account this can be explained as follows. Instead of producing the same set of possible prediction over and over, scientists in this experiment experienced had their predictions decomposed bringing about an increase in possible states. One of these new higher detailed possible predictions is what caused their breakthrough.

Indeed, the secret of genius might be the ability to carry the young brain’s ability into old age occasionally decomposing the brains stable categorical predictions to allow for added creativity and problem solving.

6. Theory limitations and Conclusions

Every theory has its own limitations and we wish to highlight the limitations in ours. Our theory focuses on dense band of 5-HT_{2A} receptors in layer V in pyramidal cell. It does not take into account subcortical 5-HT_{2A} receptors in the thalamus, brain stem, VTA, Amygdala and claustrum. This might be a reasonable limitation as following Vollenweider et al., (2001) it would seem that the psychedelic effects are indeed dependent on the neocortex more than sub cortical structures. In this experiment they used mice modified to genetically express 5-HT_{2A} receptors only in the cortex and found that these receptors were sufficient to produce hallucinogenic effects.

Furthermore our theory does not take into account lower distribution of 5-HT_{2A} receptors in other areas of cortex. For instance mammalian brain abundantly expresses 5-HT_{2A} receptors in input layers of V1. Nor does it take into account other receptors that psychedelics affect such as 5-HT_{1A} and others. These different receptors are likely to be responsible for the differences between one psychedelic substance and the other and further research is required to understand their effects.

Despite these limitations we believe our model could be very useful for the scientific community. Understanding how psychedelics affect the brain's predictive mechanism can help scientist design better experiments for instance by taking into account the effects of the precision of bottom up data. It can also help them interpret and explain their results as we have shown. This could also be useful for therapists and subjects/patients using psychedelic based therapy. Providing an explanation as to the reason these substances have such a powerful affect will help subjects feel safer and be able to navigate this delicate state better without the need to resolve to mystical explanations. It could also help in harm reduction and education of the general population. Our theory explains how a simple lowering of the excitation threshold of the pyramidal neurons in layer V in prefrontal, parietal and somatosensory cortex decomposes predictions from those areas which causes higher prediction errors from lower levels in the brain hierarchy. The brain's attempts to minimize these higher levels of prediction errors explain the psychedelic affects. Our model further explains the dependence on bottom-up data (setting) and inters subject variations (mindset) and also offers testable predictions regarding neural correlates.

Finally we would like to point out that while dopamine is considered to modulate precision of prediction error (Friston et al., 2012), this model suggests serotonin might have a role in modulating the granularity of predictions. Interestingly, in plants serotonin is known to regulate the root system architecture, branching the main root into a more granular structure (Pelagio-Flores et al., 2011). One might envision an evolutionary repurposing of such a mechanism to regulate the architecture of the top-down connectivity in the brain's neural network. Further research is needed in order to test this idea which might have a major implication for understanding many disorders that are known to correlate with changes in the brain's serotonin system.

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Figures

Figure1:

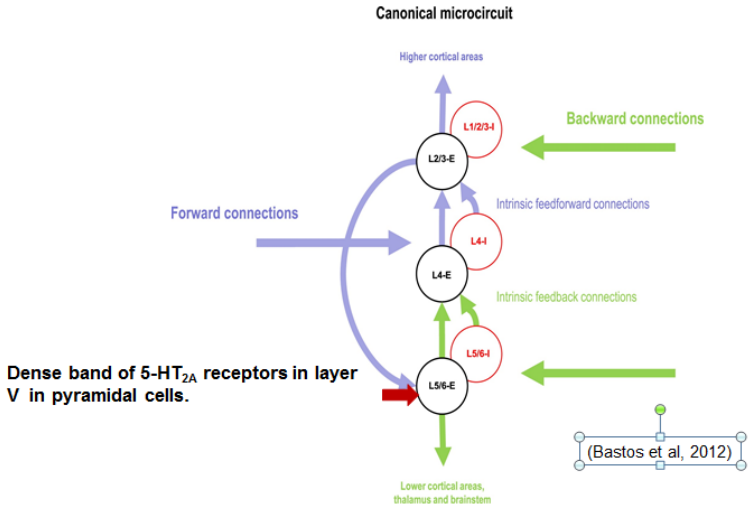


Figure 1 (Adapted from Bastos et al., 2012) : Suggested implementation of Predictive Coding in the brain. Backwards connections stem from Layer V pyramid cells that have a dense band of 5-HT_{2A} receptors.

Figure 2:

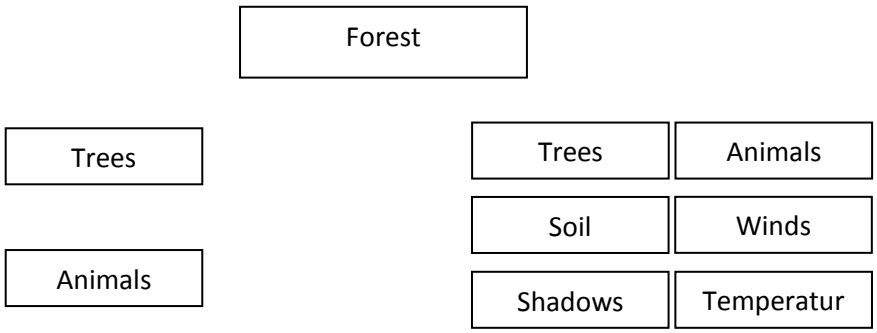


Figure 2: Predictions stemming from the category of ‘forest’ as predicted by two different individuals, a city person on the left verses a person who grew up in a forest. The granularities of subcategories that compromise the broader category are likely dependent on subjective experiences.

Figure 3:

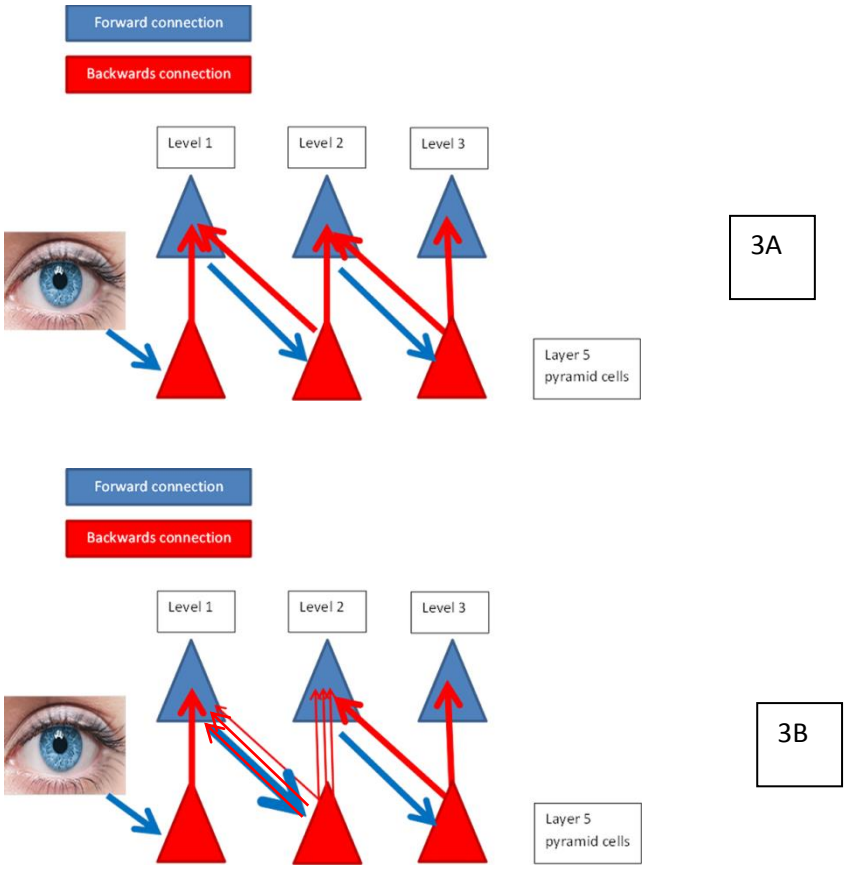
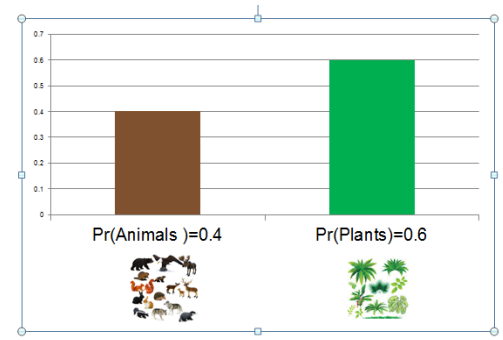


Figure 3a: under normal conditions, predictions minimize prediction error.

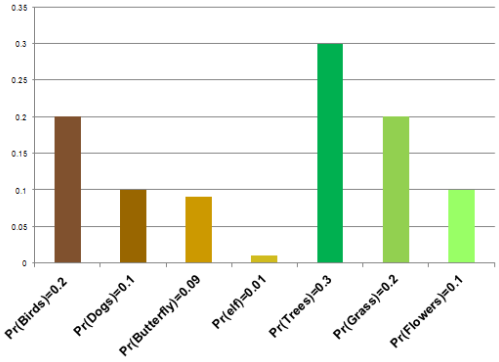
Figure 3b: After administration of 5-HT_{2A} agonist, parts of the cortex rich with 5-HT_{2A} receptors are over stimulated creating defuse predictions, resulting in higher prediction errors from lower areas.

Figure 4:



3A

Information theory entropy:
$H(P) = \sum p_i \log(1/p_i) = 0.9710$



3B

Information theory entropy:
$H(P) = \sum p_i \log(1/p_i) = 2.4933$

Figure 4A: Predictions under normal conditions. Figure 3B: Decomposed predictions after administration of 5-HT_{2A} agonist.

Figure 5:

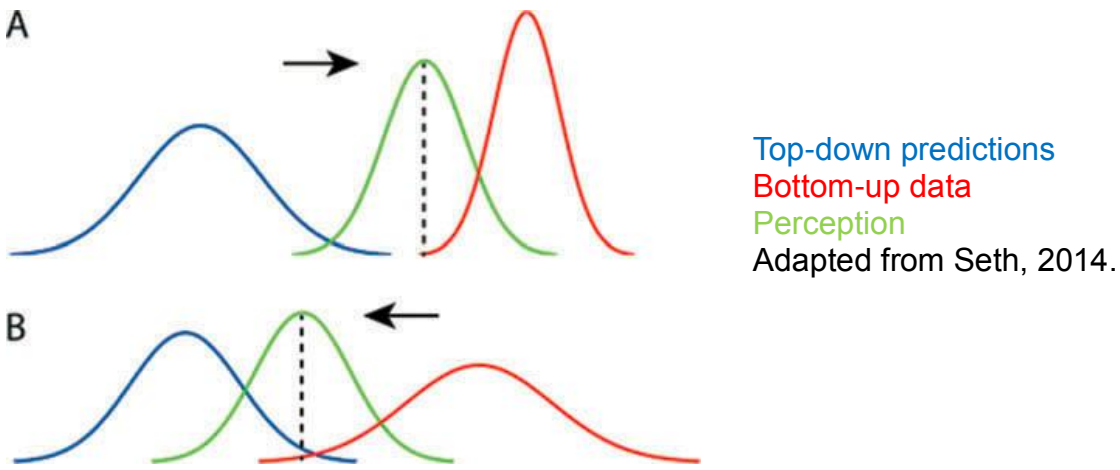


Figure 5A: accurate bottom-up data biases perception more than noisy bottom-up data. Figure 5b: Noisy bottom-up data which will be biased perception toward top-down predictions.