From hallucinations to synaesthesia: a circular inference account of unimodal and multimodal erroneous percepts in clinical and drug-induced psychosis

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Abstract

Psychedelics are known to distort perception and induce visual and multimodal hallucinations as well as synaesthesia. This is in contradiction with the high prevalence of distressing voices in schizophrenia. Here we introduce a unifying account of unimodal and multimodal erroneous percepts based on *circular inference.* We show that amplification of top-down predictions (descending loops) leads to an excessive reliance on priors and aberrant levels of integration of the sensory representations, resulting in crossmodal percepts and stronger illusions. By contrast, amplification of bottom-up information (ascending loops) results in overinterpretation of unreliable sensory inputs and high levels of segregation between sensory modalities, bringing about unimodal hallucinations and reduced vulnerability to illusions. We delineate a canonical microcircuit in which layer-specific inhibition controls the propagation of information across hierarchical levels: inhibitory interneurons in the deep layers exert control over priors, removing descending loops. Conversely, inhibition in the supragranular layers counterbalances the effects of the ascending loops. Overall, we put forward a multiscale and transnosographic account of psychosis with important theoretical, conceptual and clinical implications.

Keywords: psychedelics, DMT, ayahuasca, schizophrenia, synaesthesia, hallucinations, unimodal, multimodal, microcircuit, Bayes, circular inference.

Introduction

Hallucinations can be defined as percepts occurring while the person is awake and without corresponding external stimulation of the relevant sensory organ. Although they sometimes occur in non-clinical populations (Larøi et al., 2012), hallucinations often constitute the hallmark of psychiatric disorders, such as schizophrenia or borderline personality, and are common symptoms in neurodegenerative diseases (Waters et al., 2014). Interestingly, hallucinatory experiences can also be induced by psychotomimetic drugs.

A particular class of hallucinogenic drugs, known as "classic psychedelics" (Osmond, 1957), has fascinated scientists for more than a century. Those include naturally occurring chemicals such as mescaline (extracted from the peyote cactus), psilocybin ("magic mushrooms") and N,N-dimethyltryptamine (DMT), as well as synthetic compounds such as lysergic acid diethylamide (LSD) (Swanson, 2018). Long before the first experimental investigations with mescaline, various cultures used the psychoactive properties of these drugs either to improve the physical performance of hunters or to gain spiritual guidance (Fortier, 2018; Nichols, 2016). This is, for instance, the case of the Shipibo shamans who typically drink the ayahuasca brew (which contains DMT) while sitting in a dark place, using songs and perfumes to shape their visions (Fortier, 2018). Interestingly, those Amazonian tribes recognized the capacity of psychedelics to enhance interactions between sensory modalities long before the discovery of LSD-induced synaesthesia (Luke and Terhune, 2013).

All classic psychedelics are serotonergic agonists with a high affinity for $5HT_{2A}$ receptors (Nichols, 2004). These receptors mediate most of the psychoactive effects of psychedelics, as demonstrated by the blocking ability of 2A antagonists (e.g., ketanserin; Vollenweider *et al.*, 1998). Nevertheless, a number of other receptors, including $5HT_{2C}$, $5HT_{1A}$,

and $5HT_{5A}$ as well as dopaminergic and beta-adrenergic receptors, have also been proposed to play a role in these effects (Kozlenkov and Gonzalez-Maeso, 2013; Leptourgos et al., 2020b; Lowe et al., 2013; Vollenweider and Kometer, 2010). $5HT_{2A}$ receptors are found in both the cortex and subcortical regions but are predominantly expressed in cortical layer V pyramidal cells, suggesting a cardinal involvement of deep cortical layers in the phenomenology of psychedelics (Nichols, 2004; Weber and Andrade, 2010).

From a neurophysiological point of view, serotonergic drugs increase activity in a variety of cortical regions, including the primary visual cortex and more frontal areas (De Araujo et al., 2012; Leptourgos et al., 2020b). These serotonergic drugs also cause profound changes in the functional connectivity of the default-mode network and within/between resting-state networks and task-positive networks (Carhart-Harris et al., 2016). Finally, psychedelics can decrease the power of alpha-band oscillations (Carhart-Harris et al., 2016), which has been interpreted as an increased excitability in the absence of external stimulation (Kometer et al., 2013).

At the phenomenological level, psychedelics induce profound changes in people who consume them (Leptourgos et al., 2020b). Psychedelics notably induce perceptual, emotional and cognitive alterations (Muthukumaraswamy et al., 2013), while they can also generate mystical experiences and result in a diminished sense of self ("ego-dissolution") and a feeling of unboundedness (Griffiths et al., 2006; Halberstadt, 2015). Perceptual abnormalities comprise elementary and complex hallucinations (mostly visual or crossmodal) and intensification of visual illusions and mental imagery, together with synaesthesia (Dupuis, 2021; Leptourgos et al., 2020b), an otherwise rare perceptual phenomenon in which

activation of one modality leads to subjective experiences in other modalities as well (Hubbard and Ramachandran, 2005).

Interestingly, the content of these hallucinatory experiences (e.g., the “spirits” in the case of the Shipibo shamans) can be modulated by the activation of other sensory modalities (“effect of setting”; e.g., by singing songs or spraying perfumes). The content can also be influenced by the emotional state of the consumer prior the administration of the drug (“effect of set”; (Carhart-Harris et al., 2018)). In summary, serotonergic hallucinogens generate rich experiences, including a dominant crossmodal component (complex hallucinations with synaesthesia) and a top-down component (increased mental imagery, illusions and emotional effects) (Albright, 2012; O’Callaghan et al., 2017; Powers et al., 2016).

This description is very different from the psychotic experiences usually observed in schizophrenia (Leptourgos et al., 2020b). At the molecular level, schizophrenia has been linked to increased presynaptic storage and release of striatal dopamine (Mccutcheon et al., 2019). However, glutamatergic (Anticevic et al., 2012; Corlett et al., 2011), GABAergic (Lewis et al., 1999) and serotonergic (González-Maeso and Sealfon, 2009) abnormalities have also occasionally been associated with these dopaminergic dysregulations. At the phenomenological level, patients with schizophrenia mainly report hearing voices with dominant negative affective content, although a minority of patients also describe multisensory (usually audio-visual) hallucinations (Dudley et al., 2018; Lim et al., 2016; Llorca et al., 2016; Montagnese et al., 2021). In schizophrenia, hallucinations are regularly found coupled with a reduced sensitivity to illusions (Notredame et al., 2014).

These differences immediately raise new questions: What links exist between serotonergic agonism and the aberrant crossmodal experiences previously described? Are

drug-induced psychoses functionally and mechanistically linked to schizophrenia-related psychoses? And if so, what mechanism(s) is(are) at the roots of this phenomenological variability?

The recent renaissance of psychedelic science together with the burgeoning field of computational psychiatry (Huys et al., 2016) recently brought those questions to light, and a number of insightful theories started to address them (Carhart-Harris, 2018; Corlett et al., 2009). Despite those efforts, a unifying, multiscale account of psychosis ranging from psychedelics to schizophrenia is still lacking.

In the first section of this paper, we will integrate available findings in a unique computational framework that is able to capture the different facets of these psychotic experiences. We will notably defend the idea that *circular inference* (CI), a form of suboptimal hierarchical probabilistic inference in which likelihood and prior corrupt and amplify each other (Jardri and Denève, 2013; Leptourgos et al., 2017), can offer a holistic and functional explanation for psychoses beyond schizophrenia. Using simulations, we will show how different suboptimal inferences may be linked to various forms of hallucinations. This will allow us to propose a link between observations made at the meso-scale (e.g., erroneous messages passing) and those made at the macro-scale (e.g., behaviour and phenomenology).

In a second section, we will review empirical evidence supporting a link between meso-scale and micro-scale findings, in other words, between different forms of CI and the function of inhibitory interneurons in different layers of the cortical column. Our demonstration will build upon the critical role played by the balance between excitatory (E) and inhibitory (I) inputs in information processing within neural circuits. We state that one of the overarching goals of those interneurons is to regulate the neural E/I balance and

consequently ensure that the feedforward and feedback flows of information are not redundant.

The circular inference framework

The brain presents a highly recurrent architecture in which lateral/feedback connections dominate feedforward inputs with a ratio of 9:1 (Douglas et al., 1995). These circuits generate large levels of spontaneous neural activity (Hupé et al., 1998), directly questioning how the system disentangles self-generated signals from true/new sensory events. This problem seems particularly acute for perceptual inferences, in which sensory cues have to be integrated with prior expectations (Knill and Richards, 1996; Von Helmholtz, 1866). Such integration requires both feedforward and feedback connections (Bishop, 2006), incidentally creating internal information loops. According to the CI framework, a finely tuned balance between neural excitation (E) and inhibition (I) in neural circuits could keep the information flow under surveillance, removing all redundant messages (Jardri and Denève, 2013).

E/I balance is a well-known property of brain circuits (Denève and Machens, 2016). A dysregulation of the E/I balance could be due to impaired inhibition, too much excitation or disruptions in the neuromodulatory systems (Lucas-Meunier et al., 2009; Moreau et al., 2010; Pfeffer et al., 2018). The CI framework postulates that if inhibition is insufficient, uncontrolled recurrent excitation results in a reverberation of externally triggered sensory evidence and/or internally generated prior expectations. Such control can be insured by inhibiting redundant messages (those that have already been sent up or down the hierarchy), hence the

importance of E/I balance in predicting and cancelling recurrent excitation. Eventually (if this system is overwhelmed), the normally distinct bottom-up and top-down sources of information are corrupted by each other, and the messages are over-counted (Jardri and Denève, 2013; Leptourgos et al., 2017). A “descending loop” is defined as the corruption of the feedforward sensory information by the feedback (top-down) information, leading to an amplification of the priors. Conversely, an “ascending loop” (also called “climbing loop”) is generated when the sensory evidence corrupts the prior, leading to the amplification of the likelihood and an overinterpretation of sensory data.

Such circularity could be an important feature of perceptual inference in humans (Leptourgos et al., 2020c, 2020a), while in extreme cases, it could generate psychotic symptoms, including hallucinations and delusions (Bouttier et al., 2021; Jardri et al., 2017). This idea is in line with related theories that postulate that schizophrenia may result from an impairment in the brain’s predictive mechanisms (Adams et al., 2013; Corlett et al., 2019; Fletcher and Frith, 2009; Leptourgos and Corlett, 2020; Powers et al., 2017; Sterzer et al., 2018).

A generative model for multisensory integration

When we formalize brain function as hierarchical Bayesian inference, we assume that the brain learns the causal structure of the world. This causal structure is hierarchical (e.g., forest causing trees, tree causing leaves, etc.) and reflected in the cortical hierarchy from primary sensory areas to association areas (Jardri and Denève, 2013). Inference corresponds to the inversion of this model, e.g., determining the most likely cause of the sensory evidence.

In CI, this inference is implemented through belief propagation. For technical details about belief propagation with and without loops, please refer to the **Supplementary Material** and to relevant books and papers (Bishop, 2006; Deneve and Jardri, 2016; Jardri and Denève, 2013; Leptourgos et al., 2017).

Previous work on CI focused on simple generative models that consisted of a single stream (e.g., the pairwise graph: Forest→Tree→Leaf→Colour green, see Jardri and Denève, 2013). Those simplified models can describe hierarchical processing within one single sensory modality but are insufficient to account for crossmodal phenomena. Here, we extend these generative models by considering two parallel hierarchies, each reflecting a different sensory modality (e.g., audition (birdsong) and vision (image of a bird)). The two modalities share a common node at the top, representing a common cause (singing bird). Through this node, stimuli from multiple modalities can be integrated (e.g., merging the auditory and visual inputs caused by the same bird). Moreover, one modality can affect the other (e.g., visual identification of the bird can also predict its song). The nodes within each of the two hierarchies can be interpreted as unimodal sensory areas representing features of increasing complexity, as in the ventral stream from V1 to V4 for the visual modality. The top node could correspond to higher-order association areas where multisensory integration occurs, such as the superior temporal sulcus or the occipital-temporal junction in the case of audio-visual perception (Jardri et al., 2013, 2009; Körding et al., 2007). For illustration purposes, we will consider here the example of the stimuli triggered by a singing bird (see **Figure 1a, b**).

Inference in this graph works by iteratively calculating probabilistic messages and beliefs. In the absence of loops, sensory information climbs the cortical hierarchy, moving from sensory to association areas, and conversely prior information descends the hierarchy

(in the opposite direction). In the current model, two parallel hierarchies can talk to each other via the top node. In other words, because of this (potential) binding, the presence of a stimulus in one modality increases the probability that there is also a stimulus in the other modality (Körding et al., 2007). Once the sensory information reaches the association cortex, it does not stop there but can enter the opposite hierarchy as a prior (**Figure 2a**). In summary, each sensory modality normally receives three types of information, each coming from a different source: (i) its own sensory evidence, (ii) the sensory evidence from the other modality (computed as a prior), and (iii) prior knowledge that reaches the association cortex from the top.

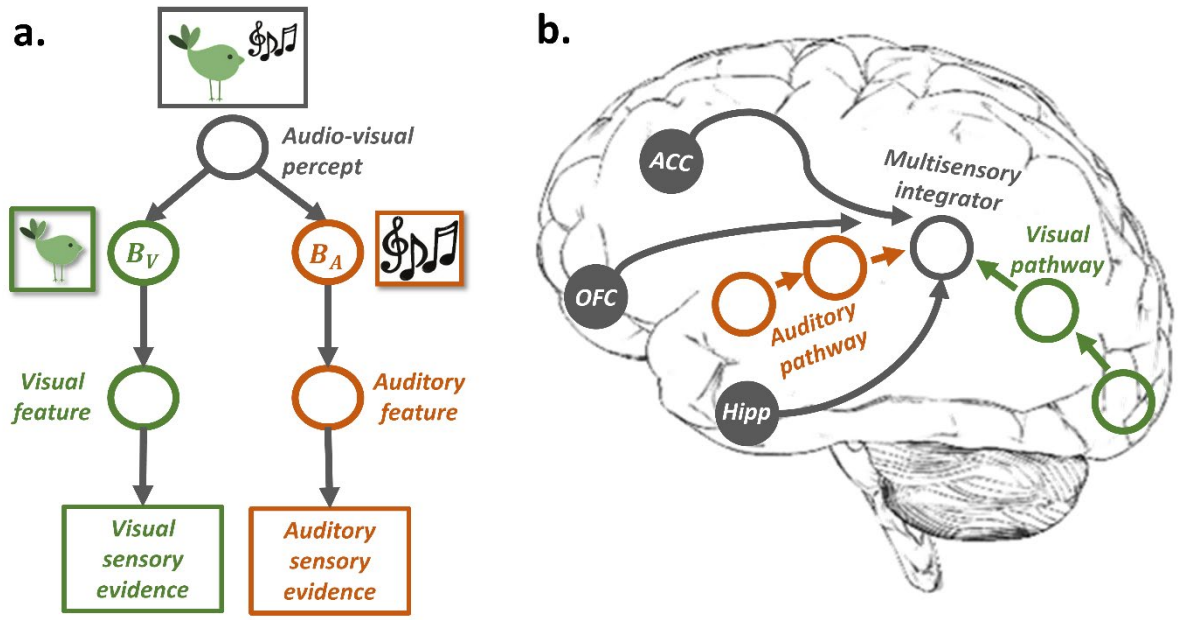

Figure 1: Generative model and cortical representation. (a): *Unlike previous formalisms of circular inference (Jardri and Denève, 2013; Leptourgos et al., 2017), here we consider a model with two hierarchies, each representing a different sensory modality (e.g., audition (orange) and vision (green)). The two modalities are connected through the top node (grey), which corresponds to the locus of*

multisensory integration (e.g., association cortex). Our example illustrates how stimulation of the two different sensory modalities might have arisen from the same "multi-modal" stimulus. Inference corresponds to the inversion of this forward model. ***(b):*** *A potential implementation of the generative model in (**a**) in the brain's hierarchical structure. According to Bayesian accounts of perception, the brain learns the causal structure of the world, which is represented in the cortical hierarchy. Filled nodes correspond to higher regions (the OFC, ACC and hippocampal complex), potentially sending different kinds of feedback information to the sensory association cortex.*

Synaesthesia, hallucinations and visual illusions

We simulated the CI framework to test the link between the meso-scale (i.e., probabilistic computations implemented by a message-passing algorithm) and the macro-scale (i.e., phenomenological varieties of the psychotic experience under psychedelics and in schizophrenia). We used a graphical model composed of binary variables representing whether a feature is present or absent. Sensory evidence activates the nodes at the bottom of the hierarchy, while priors (e.g., expectation, memory, emotions, how common is this bird) can activate the top node. To study how the different modalities interact to produce unimodal or crossmodal aberrant experiences, we separately focused on belief formation within each modality**.** Two different models were implemented:

i) A symmetrical model in which sensory hierarchies have the same structure and number of synaptic relays (**Main Text**);

ii) An asymmetrical model in which anatomical differences (e.g., in the total number of levels or the number of synaptic relays between the receptors and the level in which the belief is

constructed) generate modality-dependent aberrant experiences (e.g., mainly auditory hallucinations in schizophrenia; **Supplementary Material; Figures S3 and S4**)

We tested the robustness of the results with different parameter values (i.e., weights (strength of feedforward and feedback connections), strength of the loops, likelihoods and priors). The results were obtained after 30 iterations of the algorithm, with each iteration corresponding to one exchange of messages in both directions between all the connected nodes.

The simulations specifically covered three different scenarios:

1. In the *"synaesthesia" scenario*, we stimulated one modality (e.g., audition) with strong sensory evidence, while the other modality (e.g., vision) received weaker negative evidence.
2. In the *"sensory-driven hallucination" scenario*, both modalities were stimulated by noise, i.e., sensory evidence too weak to be considered reliable. In both cases, to avoid additional confounding effects, we did not consider any prior ($L_P = 0$).
3. Finally, in the *"perceptual illusion" scenario*, the absence of sensory stimulation was contradicted by a strong prior for the presence of a bird.

Different types of loops for different clinical phenotypes?

Scenario 1: Synaesthesia

We first explored the symmetrical model and the scenario of synaesthesia (scenario 1). This is illustrated in **Figure 2a-c**, with relevant beliefs shown in **Figure 2d, e (**see also **Figure**

S1). Here, the system receives a strong auditory activation from a birdsong (orange hierarchy) but no corresponding visual stimulation (evidence supports the absence of a bird; green hierarchy). When the system does exact inference (belief propagation without loops; **Figure 2a**), those two pieces of sensory evidence climb their respective hierarchy, reach the association cortex (i.e., the grey node) and enter the opposite hierarchy where they are fed back as priors. As expected, such a system experiences the presence of a birdsong ($P(birdsong|S_A, S_V) \gg 0.5$), but the auditory feedback to the visual area is insufficient to overcome the evidence against the presence of a visual stimulus. Thus, the system does not "see" the bird, but only "hears" it ($P(bird|S_A, S_V) < 0.5$) (**Figure 2d, e**; left bars for each modality).

The addition of descending loops results in the reverberation of messages between the two modalities (**Figure 2b**). Because of this cross-amplification, the modality receiving the strongest evidence can completely dominate the other. In visual areas, the auditory feedback overcomes the sensory evidence, and the system "sees" a bird even if its visual input says otherwise (**Figure 2d**; right bar for each modality). In the auditory modality, we observe an over-confidence (the probability of the birdsong rises higher than it should, based on auditory information alone). This is as if the "imagined" visual bird came in support of the real (but not entirely reliable) auditory information. In short, the presence of descending loops enhances the communication between the different sensory modalities, which results in a concomitant experience in the second modality, a phenomenon that corresponds to synaesthesia (Luke and Terhune, 2013).

In contrast, the addition of ascending loops degrades the communication between sensory modalities (**Figure 2c**). Information is amplified only within the modality of origin,

while information from the two modalities cannot be integrated. This makes synaesthetic experiences almost impossible. In our example, the evidence for the birdsong is amplified within the auditory modality but not the visual modality, resulting in a strong unisensory percept (**Figure 2e**, right bar for each modality).

Scenario 2: Hallucinations

In the second scenario, we explored hallucinations by considering whether strong beliefs could be generated in the absence of meaningful sensory information or prior. We thus tested the case when both modalities receive weak evidence fluctuating close to the chance level (e.g., as a consequence of sensory receptor noise, **Figure 3a, b**). Without CI, all beliefs remain close to chance, as would be expected from a Bayesian integrator.

In agreement with previous results (Jardri and Denève, 2013), loops generate strong beliefs unrooted in the available sensory evidence. However, these beliefs have unique patterns for each type of impairment. Descending loops generate a strong, crossmodal and correlated experience (i.e., multisensory hallucinations; **Figures 3a and S1b**). Both modalities strongly believe either in the presence of a singing bird (if, by chance, the total sensory evidence is slightly in favour of it) or in its absence (if the combined sensory evidence is slightly against it). When hallucinations occur, they are always audio-visual. In contrast, ascending loops result in segregated sensory modalities. Thus, if the input to one modality is by chance slightly in favour of a bird, it will develop a strong belief in that direction regardless of what is happening in the other modality. For example, the visual system can believe strongly that it sees a bird, but the auditory could believe equally strongly that it does not hear one. In that

case, the two modalities develop inconsistent interpretations of the sensory input rather than an integrated global percept (i.e., unimodal hallucinations; **Figures 3b and S1c**). Crossmodal hallucinations remain possible with ascending loops but only when unimodal aberrant beliefs co-occur by chance.

Scenario 3: Illusions

Finally, the third scenario probed the effect of a strong prior (**Figures 3c, d and S2**). If the sensory evidence contradicts the prior, this could correspond to perceptual illusions (Weiss et al., 2002). If sensory evidence is absent, it could also account for mental imagery or what we could name a prior-driven hallucination (Albright, 2012; Powers et al., 2016). Importantly, descending loops amplify the prior, resulting in more illusions and stronger mental imagery (or prior-driven hallucinations; **Figures 3c and S2b**). In contrast, ascending loops force the system to resort more to its sensory evidence, which leads to decreased susceptibility to illusions but less capacity to integrate information from multiple modalities (**Figures 3d and S2c**).

Overall, we show that while they can both lead to hallucinations, the two types of circularity generate very different phenomenological experiences. Descending loops enhance communication between sensory modalities (potentially between cognitive modules as well), leading to crossmodal hallucinations, synaesthesia, stronger mental imagery and visual illusions. On the other hand, ascending loops intensify segregation while also amplifying local sensory information, resulting in unimodal aberrant experiences, inconsistencies between beliefs in different pathways and less vulnerability to illusions. Interestingly, the former

appears closer to the clinical properties of drug-induced psychosis (psychedelics, especially the DMT-containing brew ayahuasca), while the latter shares important properties with schizophrenia. In the next sections, we will specifically investigate the links between the meso-scale and the micro-scale (neural circuits), suggesting detailed implementations for the different types of loops.

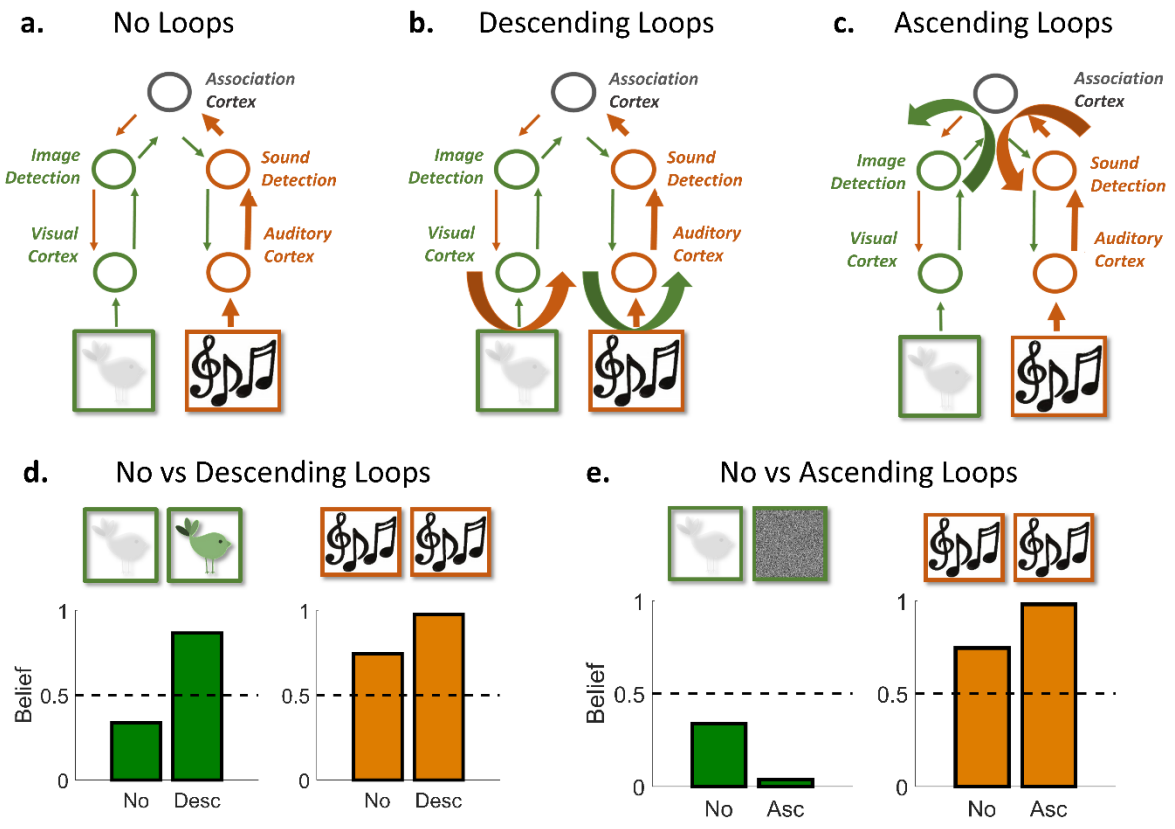

***Figure 2**: **Circular inference and synaesthesia (symmetrical model)**. **(a-c):** Belief propagation, without **(a)** and with loops **(b, c),** for the symmetrical model. In the symmetrical model, each modality consisted of 7 unisensory nodes (to keep the graphical representation as simple as possible, only 2 nodes per hierarchy were presented). The 2 modalities communicated through a multisensory node at the top. Beliefs were measured at the middle of each hierarchy (fourth node from the bottom). Information from the sensory organs climbs the hierarchy and enters the opposite hierarchy due to the multisensory*

integration occurring in the sensory association cortex. In the presence of descending loops ***(b)****, information is amplified in both modalities, rendering the two modalities almost indistinguishable. Conversely, ascending loops* ***(c)*** *force information to reverberate only inside the original modality, enhancing segregation between modalities.* ***(d, e)****: Results of simulations for synaesthesia (scenario 1). We stimulated one modality (e.g., audition) with strong, unambiguous information (e.g., birdsong;* $L_A = 2.9$*), while the other modality (e.g., vision) received negative evidence (absence of bird;* $L_V = -2$*). In the absence of loops, the system hears the birdsong (belief above 0.5) but is more uncertain regarding the presence of a bird (belief below but close to 0.5). Because of the cross-amplification caused by descending loops (****d****), the prevailing auditory information pushes both beliefs towards 1, eliciting an inversion in the case of vision. Thus, the system hears a birdsong and perceives the image of a bird, despite only audition being stimulated (synaesthesia). In contrast, ascending loops cannot generate such an inversion (or synaesthesia), because self-amplification inside the visual hierarchy reduces the visual belief towards 0 (****e****). In the presented simulations, both weights (prior and sensory weights; they correspond to conditional probabilities that quantify the strength of the reciprocal causal links between connected nodes) were taken equal to 0.95.*

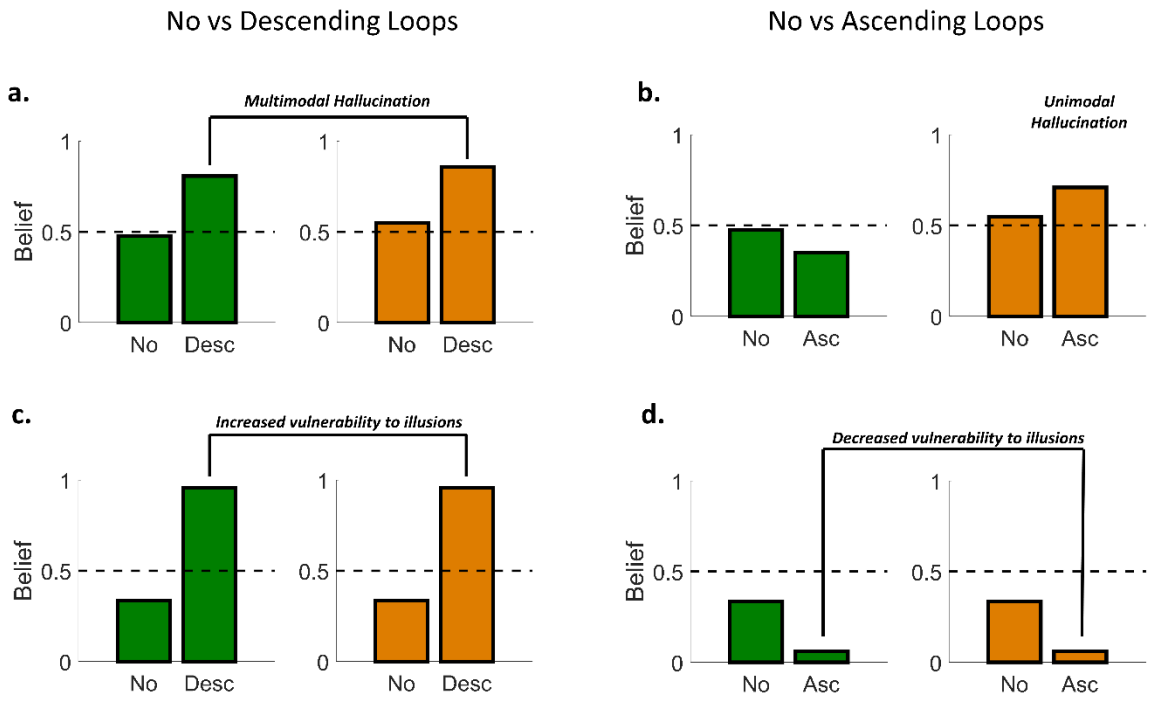

Figure 3: Circular inference and crossmodal hallucinations / illusions (symmetrical model). ***(a, b)****: Results of simulations for hallucinations (scenario 2). Unlike scenario 1, in scenario 2, both modalities were stimulated by noise (weak evidence fluctuating close to the chance level;* $L_A = 0.4; L_V = -0.3$*). Without loops, the system is completely uncertain about both the bird and the birdsong, a direct consequence of the noisy stimulation. Descending loops* ***(a.)*** *cause co-activation of the two modalities (a result of the cross-amplification), eliciting a simultaneous cross-modal hallucination. Ascending loops* ***(b)****, on the other hand, result in over-segregated modalities, which tend to rely more on their own stimulation. This results in opposite activation patterns and, more particularly, in a unimodal, auditory hallucination.* ***(c, d)****: Results of simulations for illusions / mental imagery / prior-driven hallucinations (scenario 3). In scenarios 1 and 2, the two hierarchies are stimulated only by sensory inputs (prior knowledge is absent:* $L_P = 0$*). In scenario 3, we investigate the effect of such a prior. In this particular example, we consider a prior that contradicts the sensory stimulation (*$L_A = L_V = -1.4; L_P = 1$*). Because the (contradicting) prior is weaker than the sensory information, in the absence of loops, both beliefs are below 0.5 (both the bird and the birdsong are absent; note that beliefs are equal in the two modalities because the two hierarchies are identical [symmetrical model]*

and they receive equally strong stimulation). ***(c)*** *When the prior is amplified (descending loops), inference is dominated by the feedback, resulting in beliefs close to 1 (that could correspond to an illusion, enhanced mental imagery or a prior-driven hallucination, depending on the context).* ***(d)*** *Ascending loops (amplification of sensory information) have the opposite effect (less vulnerability to illusions, weaker mental imagery and no prior-driven hallucinations) (Jardri and Denève, 2013). In all the presented simulations, both weights (prior and sensory weights) were taken equal to 0.95.*

Loops are prevented by different types of inhibition

We have highlighted that hierarchical inference depends entirely on a precise cancellation of the reverberated information, which prevents the formation of loops. Previous formulations of the CI algorithm considered a correction at the level of the messages (eq. S2).

Here, we suggest a novel formulation of the algorithm in which the correction takes place at the level of the beliefs (see **Supplementary Material** for further details).

For a pairwise graph, the resulting beliefs can be written as follows:

$$B_n^{t+1} = M_{n-1\to n}^{t+1} + M_{n+1\to n}^{t+1} - f(B_n, B_{n+1}, a_S) - g(B_n, B_{n-1}, a_P) \quad (1)$$

Messages are simply sigmoid functions of the beliefs of the sending nodes (without correction; see **Supplementary Material**), while the last two terms correspond to the subtraction of the redundant sensory (f term) and prior (g term) information.

The neural interpretation of eq. 1 is straightforward. Belief at level n is generated by integrating excitatory inputs from the levels above and below, which are balanced by inhibitory inputs from interneurons at the same level. This inhibition is driven by excitatory

neurons at the same level and the levels above or below (**Figure 4**). Crucially, the prior term (*f*) depends on beliefs at the same level and the level below. Conversely, the sensory term (*g*) depends on beliefs at the same level and the level above. This distinction speaks to an important anatomical difference between the two inhibitory mechanisms: interneurons removing descending loops are driven by lateral and feedforward connections; conversely, those responsible for control of ascending loops are driven by lateral and feedback connections (**Figure 4**).

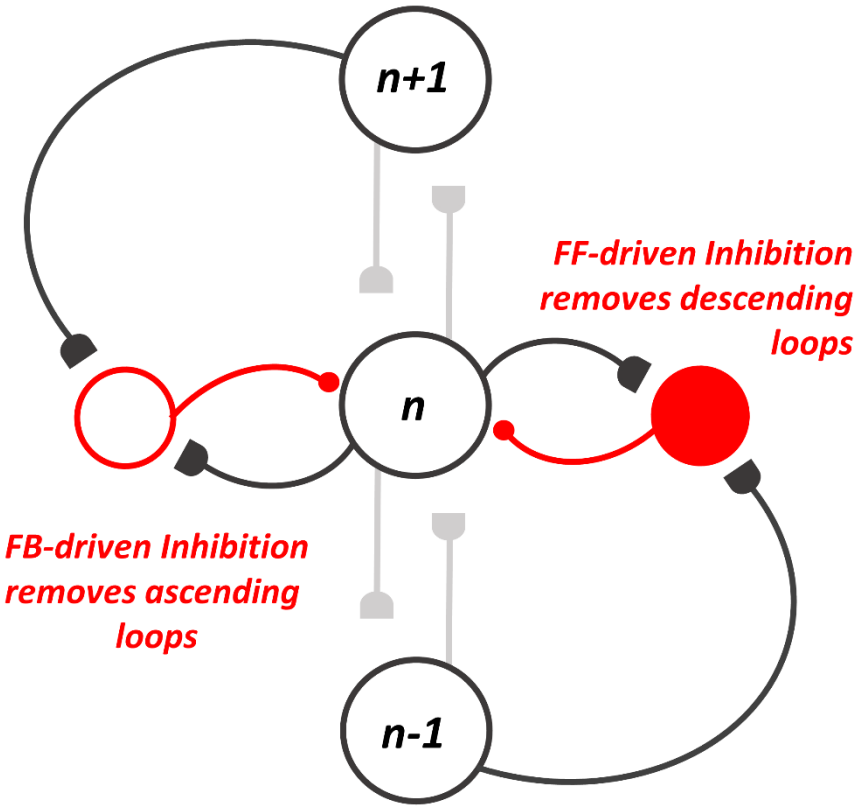

Figure 4: Different types of inhibition are responsible for preventing descending and ascending loops. *The corrections that remove redundant information can take place at the level of the beliefs, resulting in a reformulation of the circular inference algorithm. Accordingly, feedback-driven inhibition regulates ascending loops, while feedforward-driven inhibition removes descending loops (see also*

Supplementary Material *for additional information). This distinction allows us to draw links with anatomical structures implementing the different correction mechanisms. [light grey: E-E connections; dark grey: E-I connections].*

A canonical microcircuit implementing circular inference in the sensory cortex

The cortex is widely viewed as a hierarchical structure (Felleman and Van Essen, 1991), whose networks are organized in a laminar-specific manner, leading to the notion of "canonical" microcircuits (Bastos et al., 2012; Douglas and Martin, 2004). Those repeating circuits have long been viewed as the basis of many cortical computations (Haeusler and Maass, 2007; Raizada and Grossberg, 2003). What is the structure of those microcircuits and how are they linked to the CI framework?

In a cortical microcircuit, both pyramidal cells and interneurons play important roles and exhibit strong laminar specificity (Bastos et al., 2012; Dantzker and Callaway, 2000; Yoshimura and Callaway, 2005). Long-range connections consist of pyramidal cell axons, mostly targeting other pyramidal cells (Gonchar and Burkhalter, 2003). According to the dominant view, feedforward information originates from L2/3 pyramidal cells (and thalamus) and mainly targets L4, with projections onto both pyramidal cells and interneurons in a non-selective manner (Johnson and Burkhalter, 1996). These neurons then project to superficial layers (Markov *et al.*, 2014; but see also Pluta *et al.*, 2015), and from there, information reaches deep layers, especially L5 (Thomson et al., 2002). Reverse inter-laminar connectivity within an area (e.g., dashed line from L5/6 to L4 in **Figure 5**) is less frequent. Nevertheless,

strong connections exist between L5/6 pyramidal cells and L4 interneurons (Mejias et al., 2016).

In the opposite direction, feedback is less laminar specific: feedback information originates predominantly from the deep layers and targets all layers, except L4 (Kok et al., 2016; Markov et al., 2014; Muckli et al., 2015) but also non-specific thalamic nuclei (Haeusler and Maass, 2007). Importantly, many feedback connections terminate on interneurons in L2/3 (Gonchar and Burkhalter, 2003) but also in L1(Jiang et al., 2013), which then form reciprocal connections with pyramidal cells in superficial layers (Dantzker and Callaway, 2000; Yoshimura and Callaway, 2005).

Figure 5a illustrates a (simplified) canonical microcircuit implementing CI. We suggest that pyramidal cells in the superficial layers act as integrators (Meyer, 1987), receiving all the available information and generating the beliefs. This description of the cortical microcircuits illustrates in a dramatic way how the recurrent connectivity of the brain can generate information loops if inhibition fails to balance excitation (**Figure 5b, c**). In particular, feedback information re-climbs the hierarchy, generating a descending loop. For example, information sent from the superficial layers of V2 to the granular layer of V4 will be sent back due to the internal structure of the cortical column. Similarly, sensory information forms a positive feedback, involving cortical or thalamo-cortical ascending loops (Happel et al., 2014; Leptourgos et al., 2017).

More importantly, this illustration gives crucial hints about the implementation of the inhibitory mechanisms controlling the propagation of information. As described before, descending loops are balanced by inhibition driven by feedforward excitatory inputs. This description fits nicely with L4 (and potentially deep layer) interneurons (**Figure 5b**) (Parr et

al., 2019). Hypo-activation of those interneurons (e.g., because of aberrant modulation of deep layers by serotonin via $5HT_{2A}$, as observed with psychedelics) would lead to dis-inhibition of this part of the cortical circuits, resulting in an amplification of top-down messages.

Likewise, ascending loops could be balanced by feedback-driven inhibition. This description points to L1 interneurons (Bastos et al., 2012), with the possible involvement of L2/3 interneurons as well (**Figure 5c**). Impairments of inhibition in superficial layers (e.g., due to dopaminergic abnormalities in schizophrenia) would cause amplification of sensory information and thus more segregation of the sensory modalities. Note that this suggestion is compatible with the influential "dysconnectivity hypothesis" of schizophrenia (Stephan et al., 2009) and especially with a variation of this theory implicating thalamo-cortical loops (Murray and Anticevic, 2016).

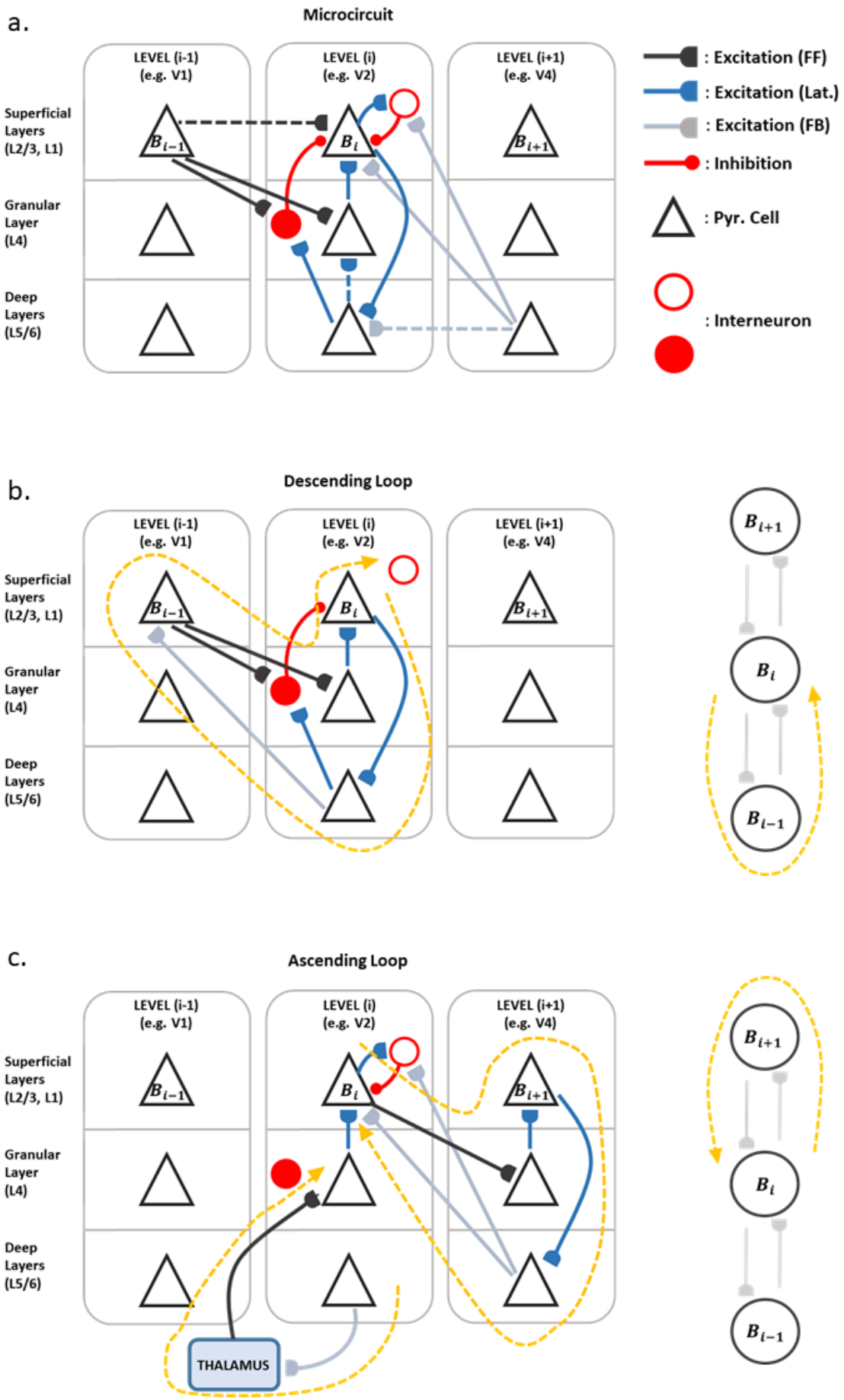
a.
Microcircuit
LEVEL (i-1)
(e.g. V1)
LEVEL (i)
(e.g. V2)
LEVEL (i+1)
(e.g. V4)
Superficial
Layers
(L2/3, L1)
Granular
Layer
(L4)
Deep
Layers
(L5/6)
B_{i-1}
B_i
B_{i+1}
: Excitation (FF)
: Excitation (Lat.)
: Excitation (FB)
: Inhibition
: Pyr. Cell
: Interneuron
b.
Descending Loop
c.
Ascending Loop
THALAMUS

***Figure 5**: **Canonical microcircuit implementing circular inference. (a):** Superficial layers act as integrators, receiving all information and generating the beliefs. Feedforward information originates from pyramidal cells in superficial layers (e.g., in V1) and targets pyramidal cells and interneurons in L4 (e.g., in V2), which then project on superficial layers. Less often, superficial layers directly target superficial layers of the level above (especially when the cortical regions are far apart). Feedback information originates from pyramidal cells in deep layers (e.g., in V4) and targets all layers except L4. Most often, it targets pyramidal cells and interneurons in L2/3 but also in L1, which form reciprocal connections with each other. Within a cortical level, superficial layers project directly on deep layers, which then drive inhibition in L4. **(b, c):** This reciprocal connectivity between levels generates loops (yellow dashed lines; ascending loop: L2/3 (V2) – L4 (V4) – L2/3 (V4) – L5/6 (V4) – [thalamus – L4 (V2)] – L2/3 (V2); descending loop: L2/3 (V2) – L5/6 (V2) – L2/3 (V1) – L4 (V2) – L2/3 (V2)), which can be avoided if inhibition successfully removes all redundant information (balances excitation). Inhibition driven by bottom-up information, mediated by interneurons in L4 (potentially also interneurons in L5/6), removes descending loops, whereas feedback-driven inhibition, mediated by interneurons in L2/3 (and/or L1), is responsible for ascending loops.*

General discussion

The goal of this paper was to delineate a CI-inspired unifying and multiscale theoretical account of false perceptions, including unimodal hallucinations (e.g. auditory-verbal hallucinations in schizophrenia), multimodal hallucinations / synaesthesia (exemplified by serotonergic agonists such as DMT) and illusions. Overall, we argue for a link between the macro-scale (behavioural and phenomenological experience), the meso-scale (belief propagation and CI in neural networks) and the micro-scale (E/I networks in a canonical cortical microcircuit.

Previous work has linked ascending loops with psychotic symptoms, including auditory hallucinations, persecutory delusions, and jumping-to-conclusions bias, and low vulnerability to illusions in schizophrenia (Jardri et al., 2017; Jardri and Denève, 2013; Notredame et al., 2014). Additionally, we have suggested that mild (descending) loops might play an important role in normal brain function (Jardri et al., 2017) and underlie common perceptual phenomena such as bistable perception (Leptourgos et al., 2020c, 2020a). Here, we extended those ideas by showing that different loops can generate very different aberrant perceptual phenomena.

We notably showed that descending loops lead to over-integrated sensory hierarchies that result in crossmodal hallucinations, synaesthesia, illusions and increased mental imagery, all common features in psychedelic-induced psychosis (other common properties such as the effect of set or the effect of emotions on perception, could also be explained by amplified top-down effects (O'Callaghan et al., 2017)). We conclude that while ascending loops might be a prominent impairment at the roots of schizophrenia symptoms, descending loops could underlie the rich phenomenology induced by serotonergic agonists such as DMT (van Leeuwen et al., 2020).

Interestingly, this unifying framework is related to a number of different theories that have addressed the problem of psychosis (Swanson, 2018), many of which were built on the idea that hallucinatory phenomena result from impairments in predictive mechanisms of the brain (Corlett et al., 2009; Friston, 2005; Muthukumaraswamy et al., 2013; Sterzer et al., 2018). In one study, the authors suggested that enhanced priors, mediated by over-activation of deep layers, generated the subjective effects associated with psychedelics (Muthukumaraswamy et al., 2013), while in another study, the same effects were associated

with impaired bottom-up processing (combined with intact top-down processing) mediated by enhanced AMPA signalling (Corlett et al., 2009).

The present account also appears compatible with another contemporary theory of psychedelics, the entropic brain theory (EBT) (Carhart-Harris, 2018; Carhart-Harris et al., 2014; Carhart-Harris and Friston, 2019). EBT suggests that psychedelics increase the entropy of brain activity, rendering it more chaotic and susceptible to intrinsic and extrinsic influences, while psychedelics also increase connectivity between resting-state (and task-positive) brain networks, in agreement with the enhanced integration induced by descending loops (Carhart-Harris et al., 2016; De Araujo et al., 2012). Note, however, that the CI framework, contrary to EBT, is a functional theory directly derived from normative principles.

Our findings have important implications for our understanding of the neural mechanisms that implement and control perceptual inference. We delineated a canonical microcircuit implementing hierarchical inference (see also Bastos *et al.*, 2012, for a related microcircuit implementing predictive coding). Inhibitory connections are crucial in preventing CI or in let CI happen, depending on how these inhibitory connections are modulated. We argued that feedback-driven inhibitory interneurons situated in superficial layers (L2/3 and/or L1) mediate the control of the ascending loops. Conversely, inhibition in the deeper layers (L4 and/or L5/6), driven by feedforward information, is mainly responsible for regulating descending loops.

Having established theoretical ties between psychedelics and descending loops, as well as between schizophrenia and ascending loops, it's tempting, and perhaps not without some merit, to speculate about the role of neuromodulation in CI. The involvement of serotonin (through the action of the $5HT_{2A}$ receptors) in the psychotic effects of psychedelics

(Vollenweider et al., 1998; Vollenweider and Kometer, 2010) suggests a link between serotonin and the part of the circuit controlling descending loops. Similarly, dopaminergic involvement in schizophrenia (Howes et al., 2015; Mccutcheon et al., 2019) suggests that this neuromodulator (in tandem with acetylcholine (Iglesias et al., 2013; Lester et al., 2010; Vossel et al., 2014; Yu and Dayan, 2005)) could target the part of the circuit controlling ascending loops.

Importantly, the CI framework makes a number of new testable predictions. First, the CI framework offers a tentative explanation for the clinical and neurobiological variability observed in psychosis. Indeed, although a majority of patients with schizophrenia experience auditory hallucinations, approximately 30% of them also experience both auditory and visual hallucinations (Amad et al., 2014; Cachia et al., 2014; David et al., 2011; Llorca et al., 2016; Rolland et al., 2015). Additionally, even if most of the patients respond well to typical antipsychotic medication (dopamine (DA) antagonists), one in four exhibits refractory hallucinations (Sommer et al., 2012). Crucially, most of these "treatment-resistant" hallucinations still respond well to clozapine, an atypical antipsychotic characterized by a high affinity for serotonin receptors (González-Maeso and Sealfon, 2009).

Although evidence for a link between these two groups of patients (i.e., those exhibiting complex multisensory hallucinations and those exhibiting drug-resistant hallucinations) is currently very sparse (Waters et al., 2014), it is tempting to suggest that these differences could be due to different types of CI. Most schizophrenia patients, who exhibit dopaminergic (and perhaps cholinergic) dysregulation, could be predominantly impaired in their ascending loops (resulting in an overinterpretation of sensory evidence and generally weakened top-down effects). This form of schizophrenia (type A, according to

Howes and Kapur, 2014) could be modelled by the psychotomimetic effects of amphetamines (DA agonists) and improved by first-line antipsychotic drugs (mostly DA D2-receptor antagonists). In contrast, a minority of patients with associated serotonergic impairments could be affected in their descending loops (resulting in strengthened top-down effects and excessive crossmodal integration). This would lead to more audio-visual and drug-resistant hallucinations, but better responses to agents with serotonergic properties, such as clozapine or even ketanserin and pimavanserin. This category of patients could constitute a good candidate for type B schizophrenia (Howes and Kapur, 2014). Some recent case studies support this claim (Nasrallah et al., 2019; Sommer et al., 2018).

The aforementioned prediction also calls for an important methodological comment. Since psychosis is not a monolithic experience, a better clinical characterization is crucial, especially when building computational models with clinical applications (computational assays; Stephan *et al.*, 2015). If not taken into account, this variability could, at minimum, contaminate the results and lead to contradicting evidence (e.g., more or less susceptibility to illusions) and, at worst, lead to inefficient treatments. In particular, despite the importance of simultaneous multisensory hallucinations as a potential diagnostic tool, only a few studies have systematically studied them (Dudley et al., 2018; Lim et al., 2016; Montagnese et al., 2021). As a result, it is difficult to objectively evaluate their prevalence (as opposed to serial hallucinations), both in schizophrenia and under psychedelics (Waters et al., 2014).

A second important prediction of the model comes from the fact that descending loops cause over-integration and thus amplification of information in both modalities. As presented in **Figure 2**, this results in a general over-confidence, affecting both modalities. Interestingly, this is a unique prediction since different models (e.g., those based on increased

prior weights; not presented here) would only generate over-confidence in the non-stimulated modality and an under-confidence in the stimulated one; future studies, based on carefully designed behavioural tasks involving stimulation of more than one sensory modalities, will have to scrutinize and arbitrate between those competing predictions.

Finally, another testable prediction pertains to the suggested implementation of CI, in particular the laminar and input specificity of inhibition and its connection with schizophrenia (unimodal hallucinations) and drug-induced psychosis (multimodal hallucinations and synaesthesia). Although standard imaging techniques do not possess the necessary spatial resolution to test so precise predictions, recent advances in high-field laminar fMRI could make it possible to probe implementations of message-passing algorithms at the level of microcircuits (Haarsma et al., 2020; Stephan et al., 2017).

We need to acknowledge some limitations. First, a cautious approach is needed regarding the potential neural substrates of CI. For instance, the suggested microcircuit is necessarily simplified, ignoring less common connections, interneuron specificities (e.g., differences between fast-spiking interneurons and adaptive interneurons (Yoshimura and Callaway, 2005)) and within-layer details (e.g., detailed connectivity within L2/3)..

Second, the current functional account of synaesthesia constitutes a model of drug-induced synaesthesia and it was not designed to account for developmental synaesthesia (e.g., grapheme-colour synaesthesia, experienced by a small number of people without any drug consumption (Hubbard and Ramachandran, 2005)). That said, it is difficult to disregard the similarity between the descending loops (amplification of priors) and ideas such as the "disinhibited prior" proposed for developmental forms of synaesthesia (Neufeld et al., 2012; van Leeuwen et al., 2020).

Overall, we put forward a unifying, transnosographic and multiscale account of psychosis, with a special focus on psychedelics. This approach may pave the way for further investigations, such as accounting for different psychotic experiences and/or contexts of occurrence (e.g., hallucinations in non-clinical populations or people with Parkinson's disease), examining the potential neurophysiological signatures of CI in humans and linking the results to animal models.

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Competing interests

The authors report no competing interest

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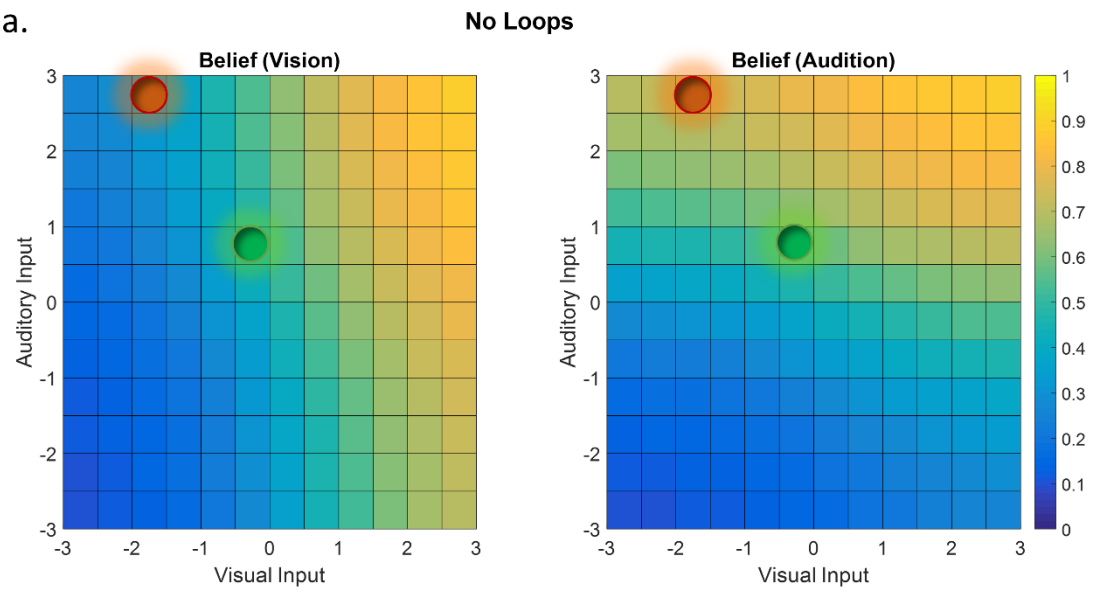
From hallucinations to synaesthesia: a circular inference account of unimodal and multimodal erroneous percepts in clinical and drug-induced psychosis

Supplementary Material

Supplementary Material 1: Additional simulations for the symmetrical model

All the scripts used for the simulations (different scenarios; symmetrical and asymmetrical model) are available at: https://github.com/VincentBt/A-multiscale-approach-to-psychedelics-based-on-the-circular-inference-framework_IMPLEMENTATION

a.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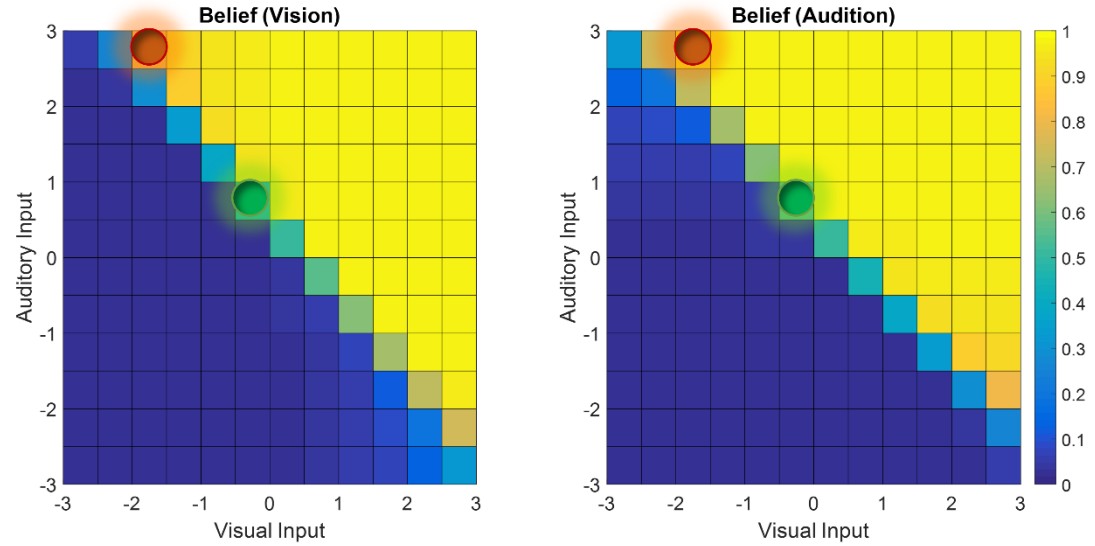
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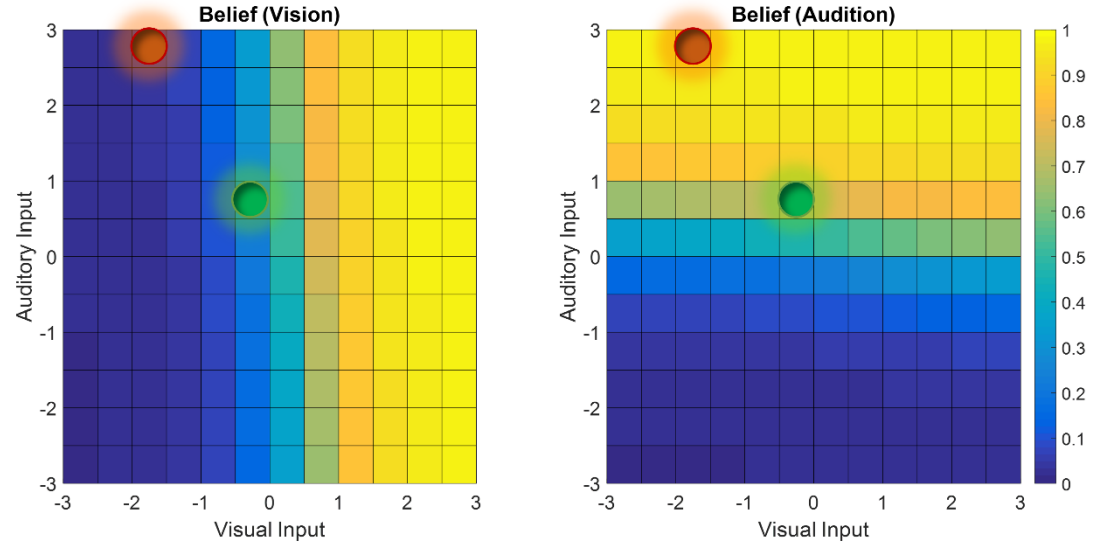
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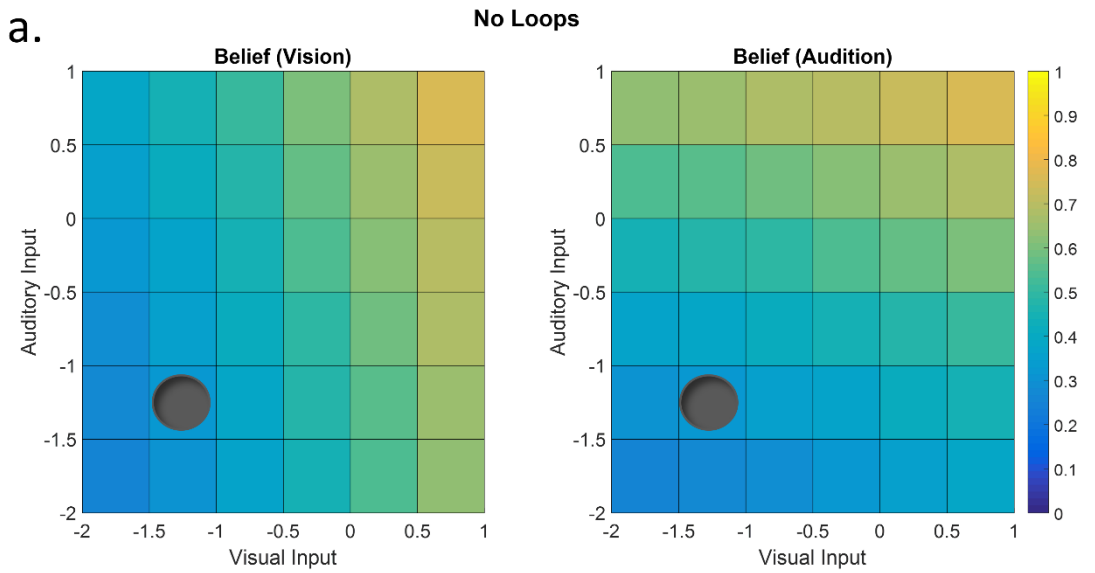
Figure S1: Beliefs as a function of sensory stimulation of the two modalities in the case of a symmetrical model. This figure is a generalization of the specific results presented in **Figures 2 and 3a, b**, with $L_P = 0$ (no priors) and $w_S = w_P = 0.95$. Each row illustrates a different type of circular inference (**(a)**: no loops; **(b)**: descending loops; **(c)**: ascending loops), while columns represent the beliefs generated within the 2 sensory hierarchies (left: vision; right: audition). The red dot corresponds to the values used in **Figure 2** (scenario 1 - synaesthesia) and the green dot to the values used in **Figure 3a, b** (scenario 2 - hallucinations). In agreement with the results presented in the **Main Text**, without loops **(a)**, the system generates moderate beliefs, which are proportional to the strength of the sensory stimulation, while integration of the sensory inputs is restrained. The addition of loops **(b, c)** disproportionately increases the beliefs, resulting in high levels of confidence even in the absence of meaningful stimulation (i.e., hallucinations). In terms of integration, the different types of loops have opposite results: descending loops **(b)** cause over-integration of the sensory modalities, which become almost indistinguishable (synaesthesia and simultaneous multi-modal hallucinations). In contrast, ascending loops **(c)** result in more sensory segregation, with the sensory hierarchy being completely overwhelmed by their own stimulation and ignoring inputs from other modalities.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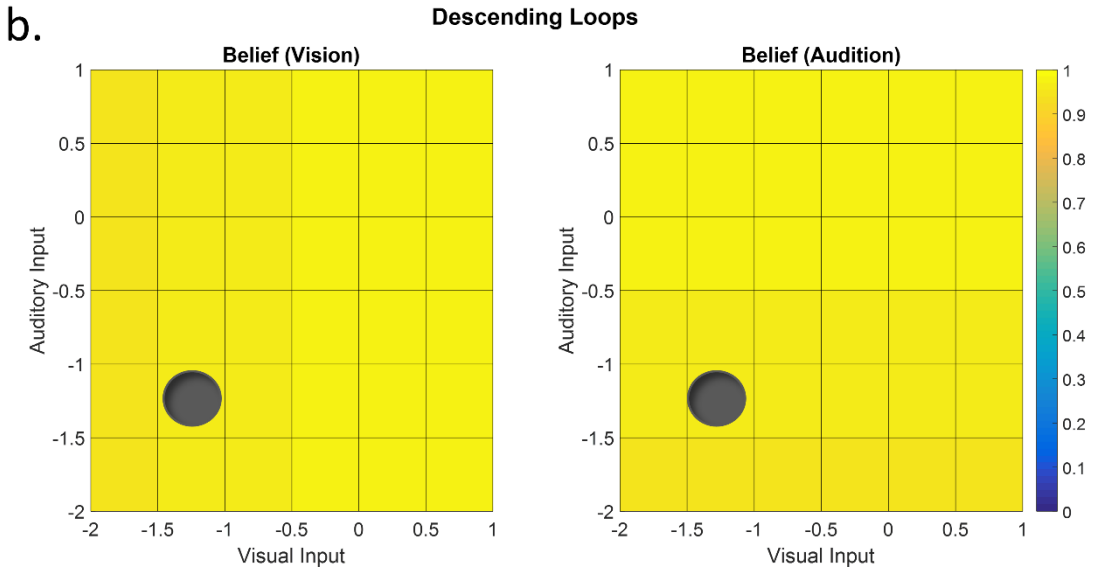
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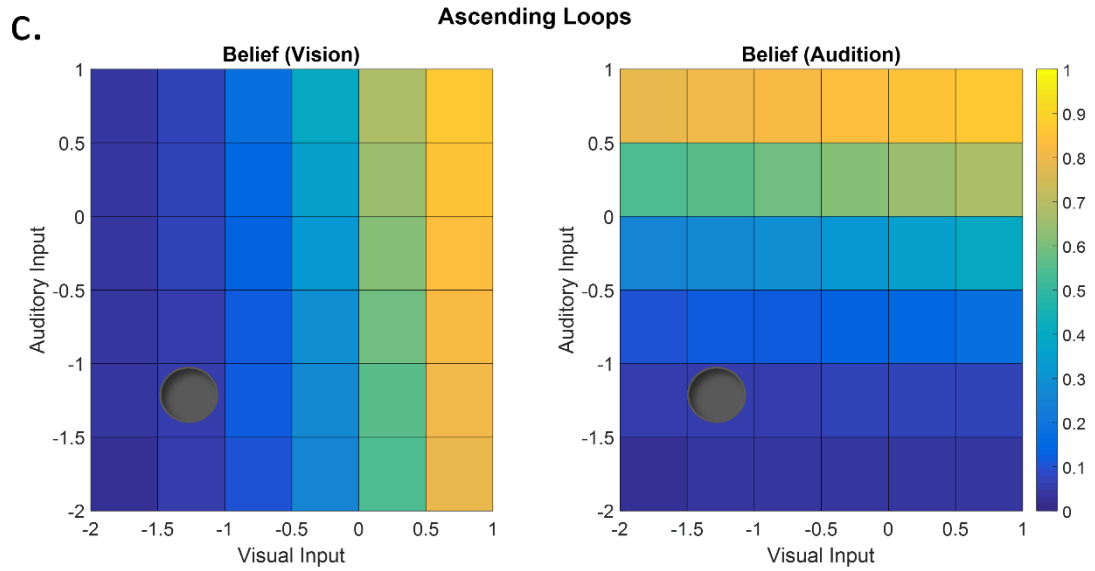
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Figure S2: Beliefs as a function of sensory stimulation of the two modalities, in the case of a symmetrical model with priors. Like **Figure S1,** this figure generalizes the simulations presented in **Figure 3c, d**, with $L_P = 1$ (there is prior knowledge) and $w_S = w_P = 0.95$. Different rows / columns correspond to different types of circular inference / modalities. The grey dot corresponds to the values used in **Figure 3c, d** (scenario 3 - illusion). Without loops **(a)**, illusions can occur only when sensory inputs are weak (compared to the priors). The addition of descending loops **(b)** results in a system that over-relies on its prior (due to prior amplification) and consequently becomes truly vulnerable to illusions (it also experiences stronger mental imagery and potentially prior-driven hallucinations). In the case of ascending loops **(c)**, the amplification of sensory inputs renders the system less susceptible to illusions / mental imagery / prior-driven hallucinations.

Supplementary Material 2: Asymmetrical model

It has been suggested that the specificity in the modalities involved in the different hallucinatory (or synaesthetic) experiences (e.g., auditory hallucinations in schizophrenia; auditorily induced, audio-visual synaesthetic experiences with psychedelics) could be a by-product of the anatomical specificitiesof the sensory hierarchies (Jardri and Denève, 2013). To test this assumption, we explored the behaviour of a model with structurally different modalities (see **Figure S3a** for details). The asymmetrical and the symmetrical models behaved in a similar manner, with two important exceptions. First, synaesthesia due to descending loops occurred only in one direction (i.e., from the modality in which the belief was generated closer to the sensory level (audition) to the modality in which the belief was closer to the top (vision)) (**Figures S3b, c and S4**). Second, unimodal hallucinations due to ascending loops were more prominent in the modality in which the belief was generated further from the top of the hierarchy (auditory modality), leaving the other modality practically unaffected (**Figures S3d, e and S4**).

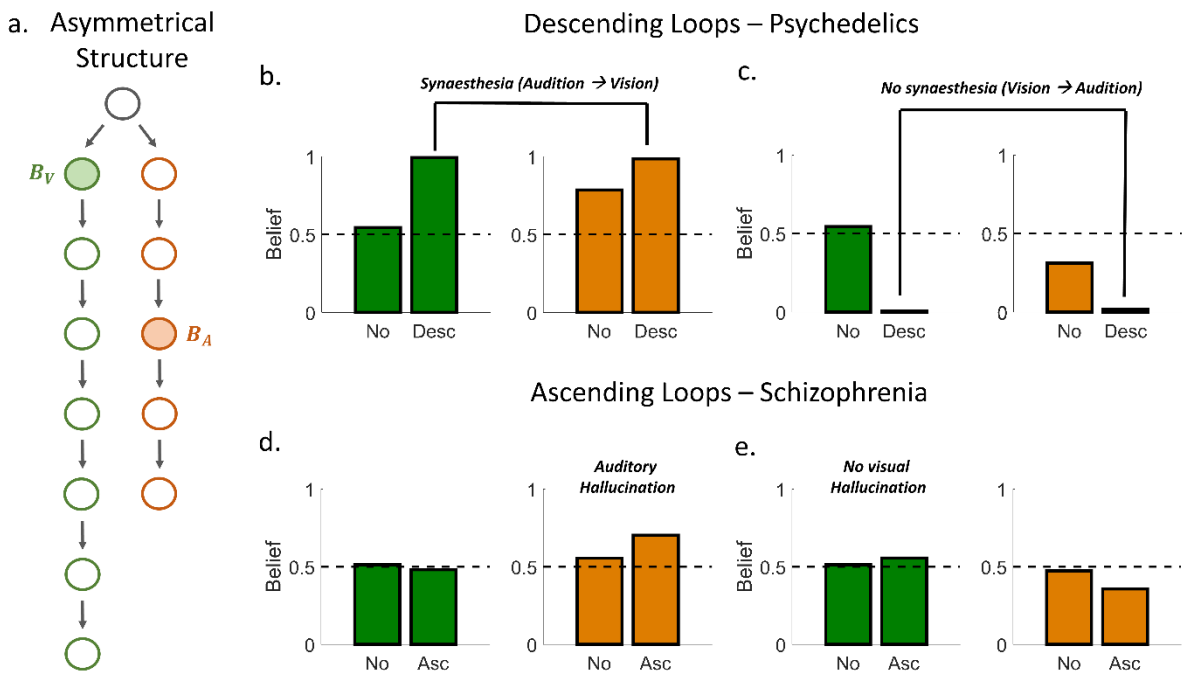

Figure S3: Synaesthesia and hallucinations in the asymmetrical model. It has been suggested that hallucinations and synaesthesia (in schizophrenia or drug-induced psychosis) are modality-dependent (e.g., patients with schizophrenia experience mostly auditory hallucinations) due to inherent anatomical constraints in the hierarchical neural structure of each modality (Jardri and Denève, 2013). We explored this possibility using an asymmetrical model. **(a)**: The structure of the asymmetrical model. We considered 2 structural differences. First, the visual modality (in green) contains more nodes (more synaptic relays between the sensorium and the sensory association cortex) compared to the auditory modality (in orange). Second, visual beliefs are generated further from the sensorium (and closer to the association cortex). Taken together, these differences result in stronger descending loops in the visual modality and stronger ascending loops in the auditory modality. These anatomical differences have important implications for the type of aberrant experience. **(b, c)**: Simulations for synaesthesia in the case of the descending loops. Although a strong auditory stimulation can induce a concurrent visual experience **(b)**, the opposite is more difficult **(c**), in agreement with empirical data from experiments with psychedelic drugs (Luke and Terhune, 2013). This asymmetry is due to the weak amplification of the visual information inside the auditory modality (B_A is generated very close to the auditory sensory epithelium), which reduces its overall effect and leads to the prevalence of the auditory input. **(d, e)**: Simulations for hallucinations in the case of ascending loops. For synaesthesia, auditory **(d)** but not visual **(e)**

hallucinations can be generated with the asymmetrical model due to the weak amplification of visual information within the visual modality (B_V is generated at a high level, close to the sensory association cortex). In the presented simulations, both weights (prior and sensory weights) were taken equal to 0.95.

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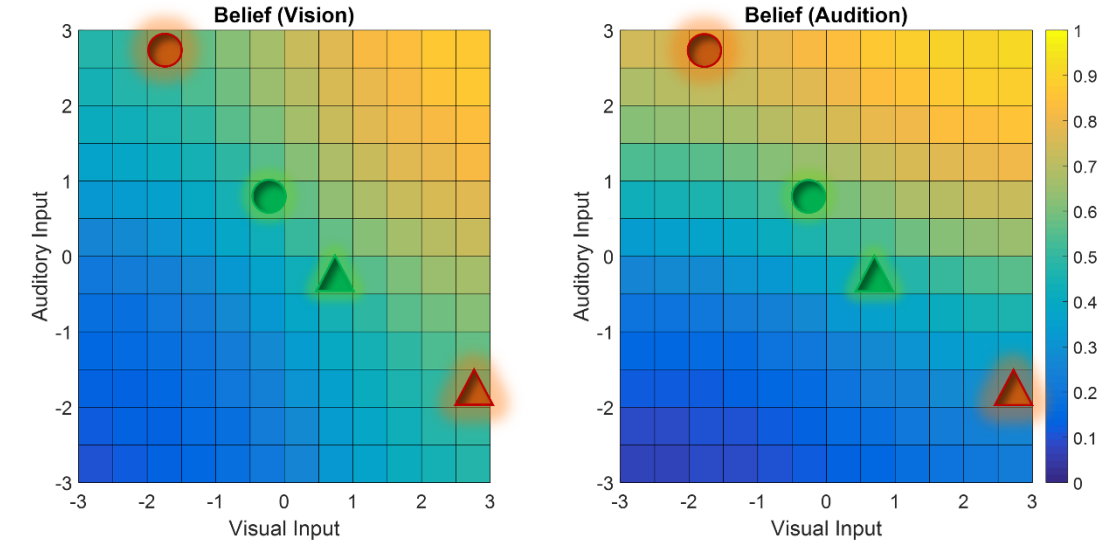
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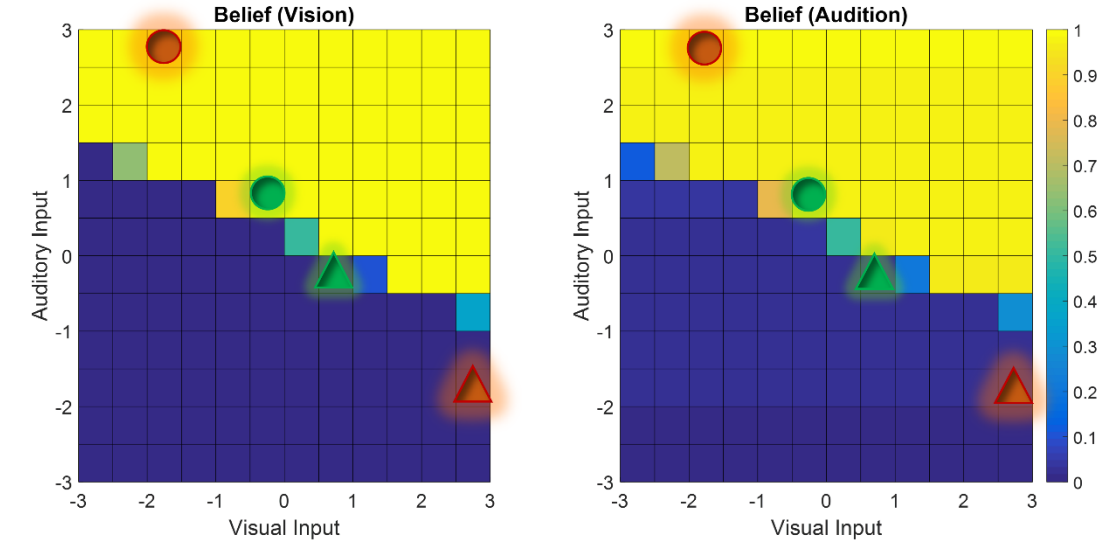
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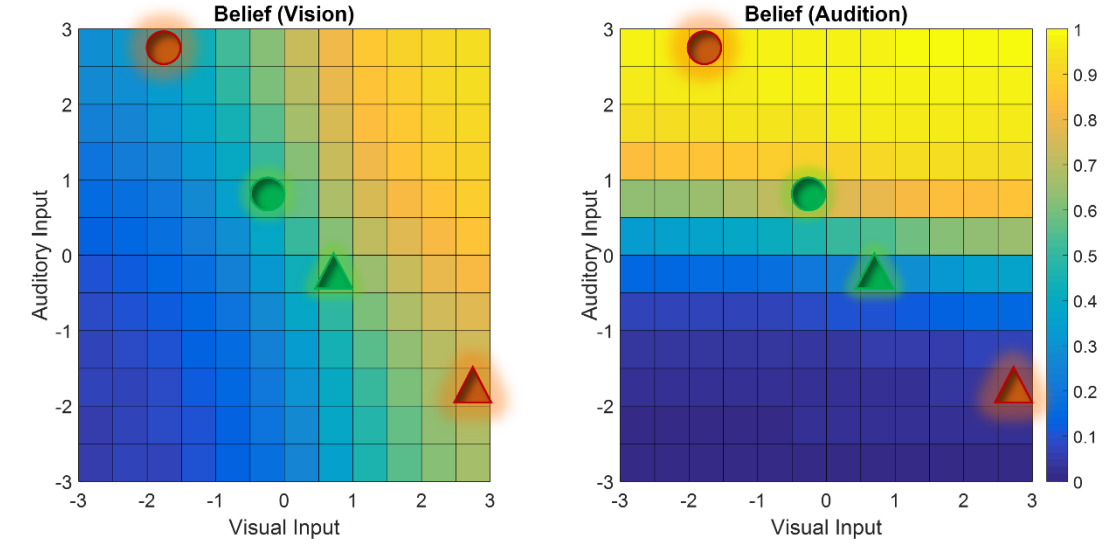
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0.6
0.5
0.4
0.3
0.2
0.1
0

Figure S4: Beliefs as a function of sensory stimulation of the two modalities, in the case of an asymmetrical model. Like **Figures S1** and **S2**, this figure is a generalization of the results presented in **Figure S3**, with $L_P = 0$ (no priors) and $w_S = w_P = 0.95$. Different rows / columns correspond to different types of circular inference / modalities. The red circle / triangle corresponds to the values used in **Figure S3b, c** (synaesthesia from audition to vision and vice versa), while the green circle / triangle corresponds to the values used in **Figure S3d, e** (auditory and visual hallucinations). Aberrant experiences are rare when the system does exact inference (no loops; **a**) but become more frequent when loops are present. Interestingly, the asymmetric model predicts asymmetric effects of the loops: auditory inputs prevail over visual inputs in the case of descending loops **(b)** and auditory but not visual amplification in the case of ascending loops **(c)**. Both weights (prior and sensory weights) were taken equal to 0.95.

Supplementary Material 3: The reformulated CI algorithm

In previous work (Jardri and Denève, 2013b; Leptourgos *et al.*, 2017), we suggested that the CI algorithm can be written in the following form:

$$B_n^{t+1} = \sum_{k=\{n+1,n-1\}} M_{k\to n}^{t+1} \qquad (S1)$$

$$M_{k\to n}^{t+1} = F_{k\to n}(B_k^t - aM_{n\to k}^t, w_{k\to n}) \qquad (S2)$$

where, $F(B,w) = \log(\frac{we^B+(1-w)}{(1-w)e^B+w})$ is a sigmoid function.

These two equations iteratively calculate the posterior probabilities (log-odds ratios) for each variable ($S1$) and the probabilistic messages exchanged by nodes ($S2$) in a way that draws an analogy with neural processing in recurrent hierarchical networks. Importantly, eq. $(S2)$ tells us that messages are a function of the belief of the node that sends the message, corrected by the message sent in the opposite direction. This correction is crucial because it controls the propagation of information, making sure that no message gets counted more than once (due to loops).

Despite its efficiency, this formulation has two main drawbacks. First, such a correction is difficult to implement in cortical circuits because it requires the additional calculation for each node of the k ($B_k - M_{n\to k}$) terms (e.g., using an auxiliary node per term). Given the complexity of real-life generative models, such a solution seems extremely inefficient (e.g., in terms of metabolic cost), but it also makes the system vulnerable to small perturbations (failure in any of the nodes would lead to a cascade of miscalculations, resulting in completely aberrant inferences). In addition, although it has been postulated that different mechanisms control the different types of loops (Jardri and Denève, 2013b), this formulation provides no information about their potential anatomical differences.

To account for those drawbacks, we here suggest a novel formulation of equations $(S1, S2)$, in which we assume that corrections occur at the level of the beliefs ($S1$). In

particular, we suggest that equations $(S1, S2)$ can be rewritten as follows (for more details, see **Supplementary Material 4**):

$$B_n^{t+1} = M_{n-1\to n}^{t+1} + M_{n+1\to n}^{t+1} - f(B_n, B_{n+1}, a_S) - g(B_n, B_{n-1}, a_P) \quad (S3)$$

with

$$M_{k\to n}^{t+1} = F(B_k^t, w_{k\to n}) \quad (S4)$$

$$f(B_n, B_{n+1}, a_S) = a_S F'_{n+1\to n}(B_{n+1}^t, w_{n+1\to n}) F_{n\to n+1}(B_n^{t-1}, w_{n\to n+1}) \quad (S5)$$

$$g(B_n, B_{n-1}, a_P) = a_P F'_{n-1\to n}(B_{n-1}^t, w_{n-1\to n}) F_{n\to n-1}(B_n^{t-1}, w_{n\to n-1}) \quad (S6)$$

and F' being the derivative of $F$with respect to B

Those equations also describe the iterative calculation of posteriors and messages, but now corrections appear as separate (non-linear) terms (f and g) in $(S3)$. Consequently, reciprocal excitation generates loops, but redundant information is removed by inhibitory interneurons directly targeting the neurons that calculate beliefs (pyramidal cells in L2/3, according to our microcircuit). More particularly, inhibition learns to track excitation (E/I balance) (Boerlin *et al.*, 2013), while neuromodulation might be driving this learning. Importantly, inhibition tracking excitation from the two streams (feedforward and feedback) has different properties: interneurons that remove descending loops are driven by lateral and feedforward excitation (indeed descending loops are generated between nodes n and $(n-1)$), while interneurons removing ascending loops are driven by lateral and feedback connections (from nodes n and $(n+1)$). It is interesting to highlight that both inhibitory terms (f and g) depend on beliefs in time t (B_{n+1}^t and B_{n-1}^t; previous iteration of the circular belief propagation algorithm) and in time $t-1$ (B_n^{t-1}; penultimate iteration), which could correspond to a delay in the connection between pyramidal cells and interneurons situated in the same hierarchical level. It is also worth noting that this formulation of the belief propagation / CI model can be implemented by a significantly simpler microcircuit (**Figures 4 and 5**) since there is no need for an explicit representation of messages (Jardri and Denève, 2013b; Parr *et al.*, 2019).

Supplementary Material 4: Derivation of equation (1)

Here we will consider a pairwise graph like the one presented in **Figure 4**. Similar results can be obtained for more complex graphs.

Circular inference in such a graph can be formalized in the following way (Jardri and Denève, 2013b):

$$B_n^{t+1} = \sum_{k=\{n+1,n-1\}} M_{k\to n}^{t+1} \qquad (S1)$$

$$M_{k\to n}^{t+1} = F_{k\to n}(B_k^t - aM_{n\to k}^t, w_{k\to n}) \qquad (S2)$$

where a can be replaced by a_S if k is above n and a_P otherwise. The superscript denotes the number of iteration of the circular belief propagation algorithm.

Assuming that $M_{n\to k}$<< B_k (e.g. in case there are many connections per node), we can use the Taylor expansion to rewrite eq. $S2$ as follows (for simplicity we will omit the weights w from the F terms):

$$M_{k\to n}^{t+1} \approx F_{k\to n}(B_k^t) - aM_{n\to k}^t F'_{k\to n}(B_k^t) \qquad (S7)$$

where F' is the derivative of F with respect to B.

Using $S7$ in $S1$ we get the following expression for B:

$$B_n^{t+1} \approx \sum_k F_{k\to n}(B_k^t) - a_S M_{n\to n+1}^t F'_{n+1\to n}(B_{n+1}^t) - a_P M_{n\to n-1}^t F'_{n-1\to n}(B_{n-1}^t) \qquad (S8)$$

Using again $S7$in $S8$ gives the following:

$$B_n^{t+1} \approx \sum_k F_{k\to n}(B_k^t)$$
$$-a_S(F'_{n+1\to n}(B_{n+1}^t)[F_{n\to n+1}(B_n^{t-1}) - a_P M_{n+1\to n}^{t-1} F'_{n\to n+1}(B_n^{t-1})])$$
$$-a_P(F'_{n-1\to n}(B_{n-1}^t)[F_{n\to n-1}(B_n^{t-1}) - a_S M_{n-1\to n}^{t-1} F'_{n\to n-1}(B_n^{t-1})]) =$$
$$= \sum_k F_{k\to n}(B_k^t)$$
$$-a_S F'_{n+1\to n}(B_{n+1}^t) F_{n\to n+1}(B_n^{t-1})$$
$$+a_S a_P F'_{n\to n+1}(B_n^{t-1}) M_{n+1\to n}^{t-1}$$
$$-a_P F'_{n-1\to n}(B_{n-1}^t) F_{n\to n-1}(B_n^{t-1})$$
$$+a_S a_P F'_{n\to n-1}(B_n^{t-1}) M_{n-1\to n}^{t-1} \qquad (S9)$$

We can continue replacing M from eq. $S7$ indefinitely. The more replacements we make, the better the approximation.

Because $a \in [0,1]$, here we keep only first order terms, which results in the following equation for B:

$$B_n^{t+1} \approx F_{n+1\to n}(B_{n+1}^t)$$
$$+F_{n-1\to n}(B_{n-1}^t)$$
$$-a_S F'_{n+1\to n}(B_{n+1}^t) F_{n\to n+1}(B_n^{t-1})$$
$$-a_P F'_{n-1\to n}(B_{n-1}^t) F_{n\to n-1}(B_n^{t-1}) =$$

$$= F_{n+1\to n}(B_{n+1}^t) + F_{n-1\to n}(B_{n-1}^t) - f(B_n, B_{n+1}, a_S) - g(B_n, B_{n-1}, a_P) \qquad (S10)$$

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