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Are Hallucinations Due to an Imbalance Between Excitatory and Inhibitory Influences on the Brain?

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This review from the International Consortium on Hallucinations Research intends to question the pertinence of the excitatory-to-inhibitory (E/I) imbalance hypothesis as a model for hallucinations. A large number of studies suggest that subtle impairments of the E/I balance are involved in neurological and psychiatric conditions, such as schizophrenia. Emerging evidence also points to a role of the E/I balance in maintaining stable perceptual representations, suggesting it may be a plausible model for hallucinations. In support, hallucinations have been linked to inhibitory deficits as shown with impairment of gamma-aminobutyric acid transmission, *N*-methyl-D-aspartate receptor plasticity, reductions in gamma-frequency oscillations, hyperactivity in sensory cortices, and cognitive inhibition deficits. However, the mechanisms by which E/I dysfunctions at the cellular level might relate to clinical symptoms and cognitive deficits remain unclear. Given recent data advances in the field of clinical neuroscience, it is now possible to conduct a synthesis of available data specifically related to hallucinations. These findings are integrated with the latest computational frameworks of hallucinations, and recommendations for future research are provided.

Key words: inhibition/hallucination/oscillation/sensory gating/GABA/glutamate/NMDA/Bayesian

Introduction

Neural circuits are regulated by activity-dependent feedback systems that act to maintain a precise excitatory-to-inhibitory (E/I) balance.[1] This E/I balance has been shown to play an important role in the development and maintenance of stable perceptual representations,[2] suggesting a plausible link with hallucinations. In support, many studies have shown that inhibitory deficits are linked with hallucinations. *Inhibition*, however, is a polysemic term with multiple meanings and functions. For example, not all the cognitive mechanisms falling under the rubric of *inhibition* may be meaningfully related to hallucinations.[3] In this article, we first review evidence for potential inhibitory dysfunction in (auditory and visual) hallucinations at different scales of understanding (ie, molecular level, system level, cognitive level). Given that hallucinations are a clinical feature of schizophrenia (SCZ), that literature is also reviewed so that deficits specific to hallucinations may be separated from those general to SCZ. Evidence drawn from studies in other conditions in which hallucinations occur is also provided. Second, we amalgamate this understanding with the latest computational models. Computational scale-free frameworks can provide powerful models for understanding hallucinations by allowing

the integration of macroscale findings with microscale factors that dictate the E/I balance. This knowledge carries potentially important information for understanding mechanisms of hallucinations, and recommendations for future research and practice in the field are provided in the last section.

Molecular and Pharmacological Evidence

Decreased inhibition or increased excitation is now a consistent finding in SCZ. Genetic,[4] physiological,[5,6] and postmortem[7] evidence converge to show an impairment of gamma-aminobutyric acid (GABA) transmission in SCZ. Using rodent models, the experimental blockage of parvalbumin interneurons,[8] or the suppression of their activity using optogenetic methods,[9] was shown to induce significant reductions in γ-oscillations, a finding which was replicated in humans with SCZ[5] (see also the section on "neurophysiological evidence"). Interestingly, such reduced GABAergic inhibition was related to perceptual deficits,[10] such as reduced vulnerability to contrast-contrast illusions.[11] Furthermore, global glutamate (Glu) receptor hypofunction (notably of the *N*-methyl-D-aspartate receptor or NMDA-R) in animal models was shown to cause an increase in intrinsic pyramidal cell excitability and a selective disruption of parvalbumin-expressing interneurons.[12]

Psychotomimetic models (eg, models that mimic the symptoms of psychosis), especially those based on ketamine (an antagonistic agent of NMDA-R), also support the E/I imbalance hypothesis. SCZ-like symptoms (eg, perceptual aberrations, delusional ideas, thought disorder, and changes in affect) have been described in healthy volunteers taking ketamine[13] as well as in autoimmune anti-NMDA-R encephalitis.[14] Moreover, ketamine affects the intensity and integrity of the sensory experience.[15] For both auditory and visual perception, acuity is increased and background stimuli become more salient.[15–17] Specifically, the drug was shown to bind D2 receptors and induce striatal dopamine release,[18] even if blocking D2 receptors with haloperidol prior to ketamine administration does not block ketamine-induced symptoms.[13]

Furthermore, ketamine does not routinely induce hallucinations, rather illusory percepts—alterations of stimuli that are actually present.[19] However, a recent report suggests that ketamine administration inside the MRI scanner (perhaps a form of sensory isolation) does induce auditory verbal and musical hallucinations.[20] Contrary to ketamine, LSD and other serotonergic hallucinogens induce profound visual hallucinations, together with altered sense of self and time[21] but no consistent delusions.[22] Serotonergic hallucinogens mainly act at 5-HT receptors. However, they also impact upon glutamatergic transmission[23] (and thus the E/I balance), especially in the locus coeruleus[24] and in frontal cortex.[25]

Brain Imaging Evidence

From Hyperactivation to Brain Dysconnectivity

Consistent with the notion of an E/I imbalance, metabolic and functional changes in speech-related areas have been widely reported in functional brain imaging studies of SCZ patients with hallucinations.[26] Two main study categories can be distinguished: (1) *trait studies* (ie, studies comparing hallucinators with nonhallucinators) and (2) *state studies* (ie, studies conducted during the occurrence of hallucinations in the scanner). Increased activation within a bilateral frontotemporal network was confirmed by coordinate-based meta-analysis of the auditory hallucination (AH) state.[27] State studies conducted in nonclinical hallucinators also confirmed the role of frontotemporal regions in these experiences, independently of the SCZ status.[28] Parahippocampal signal fluctuations preceding the occurrences of hallucinations,[29] as well as dysconnectivity patterns of the hippocampal complex during hallucinations,[30,31] tend to indicate a possible link between hallucinations and memory systems (see also the "Cognition" section).

Trait studies mainly explored verbal self-monitoring, verbal imagery, and source memory.[26] These experiments showed that SCZ patients with AHs exhibit decreased activation within temporal, cingulate, premotor, and subcortical regions thought to subserve the above-mentioned functions.[32] In a recent study using a predictive learning task, aberrant resting activity was evidenced in auditory cortex as well as weakened responses to unexpected speech in patients with AHs,[33] suggesting auditory cortex prediction error dysfunction.

Auditory hallucinations are also associated with impaired connectivity of large-scale networks at both the functional[34] and structural level.[35] Functional connectivity between Wernicke's area and Broca's areas, for example, is shown to be disrupted during inner-speech processing in SCZ patients who hear voices,[36] in line with the "comparator model" theory, positing that AHs are related to inner-speech self-monitoring impairments.[37–39] Overall, studies conducted in SCZ suggest that this dysconnectivity may rely at the microscale on impaired control of synaptic plasticity,[40] notably of NMDA-dependent plasticity.[41,42] Importantly, the dysconnectivity hypothesis was recently applied to specific symptoms such as hallucinations, eg, comparing different SCZ subgroups that only differ on their hallucination status (ie, with or without hallucinations, but also with unisensory or multisensory experiences),[30,43] and to hallucinators outside of this clinical spectrum.[44] Changes in distributed functional connectivity networks were finally obtained when targeting the left temporoparietal junction with noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (TMS),[45] or transcranial direct current stimulation (tDCS),[46] with

substantial impacts on AH severity (see also the section on "neuromodulation studies").

Glutamate and MR Spectroscopy

Given that Blood-Oxygen-Level Dependent fMRI (fMRI-BOLD) activations correlate with increases in Glu concentrations,[47] we could expect that Glu abnormalities overlap with the above-mentioned increases in neuronal firing during AHs.[27,32,48] Studies show Glu concentration abnormalities in SCZ relative to healthy controls,[49,50] but very few studies have made the link to AHs. An exception is a recent study using a MR spectroscopy (^{1}H-MRS) approach. Hugdahl et al[51] demonstrated reduced Glx levels (ie, the sum of Glu and Glutamine, Gln) in the posterior temporal lobe and the inferior frontal gyrus of SCZ participants relative to healthy controls. A significant positive correlation was also found between frontal-temporal Glx levels and hallucination severity (assessed with item P3 from the Positive and Negative Syndrome Scale, PANSS), while correlations with negative symptoms were close to zero. Interestingly, the Glx levels were higher in patients that scored in the upper range of the P3 symptom range, which was interpreted as linked with a glutamatergic hyperactivity, not inhibited by the corresponding increase in GABA release. This would mean that AHs may be accompanied by Glu increase, rather than Glu reduction. A recent meta-analysis of ^{1}H-MRS in SCZ also suggested that illness phases were associated with different Glu profiles.[50] Increased metabolite concentration in the speech areas in the temporal lobe was also reported by Homan et al[52] when comparing hallucinating and nonhallucinating patients.

Neurophysiological Evidence

Phase Synchronization

Neurons have been shown to synchronize their oscillatory phase ("phase synchronization") in response to specific stimulus contexts.[53] This phenomenon depends critically on E/I balance and is thought to provide a temporal code that underpins coherent perception, thought, and action (the "binding problem"), which has now been observed within and between distributed brain structures during rest, encoding, and higher-order cognition.[54–56]

State studies have typically observed increased phase synchronization in the auditory cortices of SCZ subjects. Initial case reports linked AHs to increased γ-band activity in left auditory cortex,[57,58] while larger works have reported increased α-band synchrony between right and left auditory cortices,[59,60] and more recently of θ-band and γ-bands in left frontal and auditory cortices.[61] Ford and colleagues[38] found 150 ms prior to and until speech production that β-band synchronization (~15 Hz) was larger over frontal cortex in HC compared to SCZ; the degree of synchrony in controls was positively correlated with the degree of auditory N1 amplitude suppression resulting from corollary discharge (N1 amplitude during talking versus listening), while in SCZ lower synchronization was related to AH severity.

Several trait studies have examined neural synchronization using auditory steady-state response (ASSR) paradigms. Spencer and colleagues[62] found that 40 Hz stimulation elicited reduced γ-band synchronization in left auditory cortex of SCZ compared to HC, but was modulated by δ-band (2 Hz) activity in SCZ. The degree of γ-band synchronization was also related to the lifetime experience of AHs in SCZ. Reanalyzing the same data, Mulert and colleagues[6] found that greater synchronization between bilateral primary auditory cortices was correlated with AH severity in patients.

Using 20, 30, and 40 Hz stimulation, Koenig and colleagues[63] found that a global measure of phase-locking was increased during ASSR stimulation in non-AH patients and healthy subjects (especially at 40 Hz), but was decreased in AH patients, notably in the left hemisphere. Subsequently, these authors found that the time to peak "late-latency" γ-band amplitude (early-gamma = 0–100 ms, late-gamma = 200–300 ms), irrespective of phase-locking, distinguished AH from non-AH patients (ie, AH longer), and that longer time to peak was positively correlated with AH severity.[64] Using a similar paradigm, Hirano and colleagues[65] also found that phase-locking was significantly reduced in SCZ compared to controls at 40 Hz only, however, non-phase-locked mean γ-band power (amplitude) was not different between the groups at rest and was increased during 40 Hz ASSR stimulation in SCZ. Also in SCZ, AH symptoms were positively correlated with induced 40 Hz γ-band power in the left hemisphere and negatively correlated with the ASSR stimulation phase-locking factor.

Sensory Gating

Sensory gating, a form of preattentional inhibition when facing repeated sensory stimulation, is usually examined with pairs of stimuli (S1 and S2) presented at some stimulus-onset-asynchrony (SOA). In healthy subjects, a positive wave peaking ~50 ms after each stimulus (P50), exhibits reduced amplitude to S2 compared to S1; the S2:S1 "gating ratio" of P50 amplitudes is the dependent measure in clinical studies. Acutely psychotic and non-psychotic SCZ patients exhibit larger P50 gating ratios than healthy controls (especially when SOA = 500 ms), irrespective of medication status.[66,67] This deficit is also observed in about half of SCZ relatives,[68] indicating that a P50 gating ratio deficit may be a endophenotypic marker for vulnerability to SCZ.

Two studies have explored the role of impaired sensory gating in AHs. Using a standard paradigm, Smith

and co-workers[69] observed greater P50 in SCZ with drug-resistant hallucinations compared to healthy controls, and SCZ ratios exhibited a positive correlation with lifetime AH scores (from the PSYRATS) but not current AH scores (from the PANSS). In contrast, Hirano and colleagues[70] found that the magnetic P50 (P50m) gating ratio analogue observed in response to pairs of a Japanese vowel sound (SOA = 500 ms), was larger in the left hemisphere in SCZ compared to healthy controls, and was positively correlated with current AH scores, however, not all SCZ had drug-resistant hallucinations.

Neuromodulation Studies

Combining TMS with electroencephalography (EEG) and electromyography constitutes a powerful tool to assess the E/I balance in humans.[71,72] Numerous studies have investigated excitatory and inhibitory mechanisms in medicated, unmedicated, first-episode patients with SCZ and subjects at risk to develop SCZ,[73] but only few studies have investigated their relationship with AHs.

Most of paired-pulse TMS paradigm applied over the motor cortex investigating NMDA glutamate receptor activity failed to demonstrate any difference between SCZ patients and healthy controls.[74,75] No studies directly explored the relationship between AHs and excitatory mechanisms measured by paired-pulse TMS paradigm applied over the motor cortex. Investigating the parieto-motor connectivity with a subthreshold preconditioning pulse over the posterior parietal cortex before the test pulse over the ipsilateral motor cortex, a study reported reduced paired-pulse facilitation in patients with SCZ.[76] Even if such facilitatory interactions are thought to depend on the superior longitudinal fasciculus integrity, a white matter tract associated to AHs' severity,[77] patients with lower negative symptoms had less impaired parieto-motor connectivity.[76]

Short-interval cortical inhibition (SICI) is a paired-pulse paradigm with 1–4 ms interstimulus intervals associated with the GABA-A receptor-mediated inhibitory neurotransmission.[78] A recent meta-analysis[74] reported that SICI was significantly reduced in SCZ patients when compared with healthy subjects (d = 0.476). Daskalakis and colleagues reported that the intensity of the SICI deficit correlated with the intensity of positive symptoms.[79] Investigating integrity of the cerebello-thalamo-cortical loop with a TMS pulse delivered over the cerebellum 5–15 ms before a TMS pulse applied over the contralateral primary motor cortex, a study also reported reduced cerebellar inhibition in SCZ patients.[80] Even if cerebellar dysfunction has been linked with confusion between reality and perceived reality, leading to positive psychotic thinking,[81–83] the relationship between the severity of AHs and the intensity of the cerebellar inhibition deficit has yet to be explored.

Combining TMS and EEG, Farzan and colleagues[84] reported that patients with SCZ had significant deficits in the inhibition of gamma oscillations in the dorsolateral prefrontal cortex, a phenomenon known to be associated with an impairment in GABA-B receptor-mediated inhibition. The severity of this deficit correlated with the illness severity as measured by the Brief Psychiatric Rating Scale (BPRS). However, the specific link with AHs was not investigated. Interestingly, using tDCS, a recent study also investigated the excitability of the occipital cortex in healthy subjects, and reported a correlation between the predisposition to anomalous experiences/hallucinations score measured by the Cardiff Anomalous Perceptions Scale (CAPS)[85] and the number of visual distortions that occurred from viewing aversive gratings during active and sham tDCS.[86] This suggests a hyperexcitability of the brain in clinical and nonclinical subjects predisposed to hallucinate.

Cognition

Inhibition is also a broad psychological construct which refers to a particular form of prefrontal executive control that assists a range of cognitive skills (ie, attention, learning, memory, and language) and behaviors. The principal role of cognitive inhibition is to suppress irrelevant information and previously activated cognitive contents, and resist interference from competing stimuli.[87] Cognitive inhibition can be further differentiated into (1) *interference control* which refers to an initial perceptual stage of processing[88] (assessed on tasks such as the Stroop task); (2) *automatic (or unintentional) inhibition*, referring to automatic, preparatory, and prestimulus processes[89] (assessed with tasks such as Negative Priming paradigms[90]); and (3) *intentional inhibition* which applies to goal-directed and poststimuli processes which may be conscious or unconscious[89,91] (assessed with tasks such as the Hayling Sentence Completion Task [HSCT] or the Inhibition of Currently Irrelevant Memories Task [ICIM][92]).

By definition, AH in SCZ are sensory experiences over which the person does not feel (s)he has direct and voluntary control.[93,94] Consequently, cognitive explanations of AH have suggested that this reduced sense of control arises from a breakdown in inhibition,[95] and that such deficits might result in the emergence of irrelevant material from long-term memory into awareness.[96,97] In support, studies have showed that hallucination frequency in SCZ was associated with difficulties on tasks requiring the suppression of irrelevant information and distracting information, like the ICIM and HSCT tasks,[98,99] a Directed Forgetting (DF) task,[100] and the Dichotic Listening task,[101] all pointing to deficits in intentional inhibition. Such deficits were not correlated with delusions or other symptom dimensions. Similar deficits have been found in Alzheimer disease patients with hallucinations[102] as well

as with nonclinical groups who score high on a measure of hallucination proneness.[103,104] Mental health conditions that are characterized by unwanted and uncontrollable cognitions, primarily obsessive compulsive disorder (OCD)[105–107] and posttraumatic stress disorder (PTSD),[108–111] also show similar deficits in inhibiting mental events.

Studies also show selective impairments in the domain of intentional inhibition, but not in the other inhibition constructs referring to interference control and automatic inhibition.[112–115] Such dissociations suggest that deficits may be specific to the deliberate suppression of salient cognitive representations, in contrast to motoric or unconscious responses. This notion is consistent with early theories of hallucinations, proposing that they involve "parasitic memories"[116,117] or the intrusions of strongly activated (but irrelevant) representations in memory,[96,97] especially when words are negative or derogatory.[118]

Two studies extended these results in nonclinical participants scoring high on measures of hallucination-like experiences. Paulik et al[103] reported that these individuals made more false alarms on ICIM conditions requiring intentional inhibition than comparison controls. This finding was partially replicated by a recent paper,[104] which showed correlations between ICIM scores and participants' scores on one measure of hallucination proneness (the Cardiff Anomalous Percepts Scale; $r = .38$) but not with another (the Launay-Slade Hallucination Scale; $r = .10$). Thus, in both clinical and nonclinical groups, there is evidence to suggest that the predisposition to hallucinate is related to intentional inhibition abilities.

Considering These Findings Using Scale-Free Computational Approaches

Building on the previous sections, the following considers how both micro- and macroscale findings on hallucinations can be convincingly articulated using computational modeling. Several theoretical models have already been proposed to account for hallucinations.[119,120] In this report, we will mainly focus on Bayesian inference, but note that the different underlying hypotheses behind these computational frameworks (eg, attractor states, noise models, etc.) are not necessarily mutually exclusive but perhaps complementary, in that they bring different insights into the mechanisms behind hallucinations.[121]

The Predictive Coding Framework

Recent theories propose that hallucinations could be due to altered inference mechanisms.[122–124] Originating from Helmholtz' idea of unconscious inference,[125] these theories conceptualize the brain as an inference machine that uses learned predictions (prior beliefs), combined with sensory evidence, to infer the causes of the incoming sensory data ("posterior probabilities"). Importantly, both the prior and the sensory evidence are weighted by their precisions, which define their relative contributions on the "posterior."

A plausible implementation of Bayesian inference in the brain is hierarchical predictive coding.[126–129] The core idea is that an internal model that represents the knowledge about the outer world serves to generate a stable perceptual experience despite noisy sensory data. Predictive signals are thought to be fed back from higher to lower levels of the cortical hierarchy. When these predictions are violated by the sensory data, a precision-weighted prediction error signal is fed forward to the next hierarchical level to update the predictive model and drive learning. If the precision of the sensory data is high relative to the precision of the prior belief, the prediction error will be greater, and vice versa. It has been proposed that psychosis is linked to increased prediction error signaling[122] which in turn leads to aberrant salience and the formation of delusions, as proposed earlier.[123,124,130–132]

Disrupted predictive coding has also been invoked as a mechanism underlying hallucinations per se.[122–124] Different predictive coding alterations have been proposed. One possibility is that hallucinations result from an overly strong effect of top-down predictive signals on neural activity in sensory cortices.[133,134] Others have linked hallucinations to a failure to attenuate the sensory consequences of inner speech, in analogy to the mechanism that is thought to underlie delusions of control.[42,124,135] In Bayesian inference terms, the latter mechanism would correspond to increased *prediction errors*, possibly resulting from neural signals that encode inner speech in auditory cortex with relatively high precision.[122,136] Even if compatible with the E/I imbalance hypothesis, how this expectation gives rise to voices rather than other sounds remains to be established.[137]

The Circular Inference Framework

The *prediction coding* hypothesis suggesting that SCZ subjects give too much relative weight to their prior beliefs may have some limitations, especially when considering the fact that patients with psychosis are *less* sensitive to many perceptual illusions than healthy individuals,[11,138–140] which is inconsistent with the proposition that strong priors would be at the root of perceptual illusions.[141,142] To overcome these shortcomings, it could be useful to come back to a mathematically rigorous formulation of hierarchical causal inference. In a Bayesian network, inference can be performed by a recurrent propagation of messages between causal nodes in all possible directions: top-down, bottom-up, and laterally. Inference is only complete after all such messages have been sent in the cortical hierarchy.[143] Since long-range connections in the brain are overwhelmingly excitatory, these messages would be reverberated endlessly through feedforward/feedback excitatory loops if they were not controlled by the presence of equivalently strong inhibitory

connections. Indeed such balance is tightly maintained in cortical networks, and was shown affected in SCZ.[144] Scaling down inhibition (or scaling up excitation) in such a computational model results in a pathological form of inference called "circular belief propagation," in which "bottom-up" and "top-down" messages are reverberated and taken into account multiple times.[145]

Even when facing weak sensory evidence, circular propagation generates strong perceptual beliefs: hallucinations occur where nothing relevant should have been inferred. In the same way, circular inference introduces spurious correlations between feed-forward and feedback messages that are nonexistent in the real world. This leads to the learning and consolidation of "unshakable" (but false) causal relationships, resulting in delusional belief systems. In this line, hallucinations have been proposed to originate primarily from the reverberation of "bottom-up" messages, leading to an overinterpretation of the sensory evidence.[145] This does not rule out the possibility that some individuals with hallucinations (within, but also beyond the SCZ spectrum) may overinterpret their priors.[133,146] Importantly, these 2 hypotheses could be tested experimentally by measuring how patients weigh their likelihood and priors during decisions.

Further Experimental Support

Besides the clinical and cognitive predictions of these models, several neural implementations have been proposed.[126,127,143,147–150] Regardless of its specific implementation, it is important to consider that belief propagation relies on local inhibitory control to avoid *circular inference*. The presence of these corrective connections has been shown to be highly compatible with the architecture, connectivity, and dynamics of the cortical column.[151] In such a context, it can be interesting to reappraise the effects of ketamine from an inferential point of view. Corlett et al suggested that under ketamine, the subject may experience both perceptual aberrations (due to AMPA [α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor] upregulation) and a reduced capacity to accommodate and ignore these aberrations (due to NMDA blockade).[123] This suggests that ketamine and phencyclidine (PCP) disturb the feed-forward mechanism (prediction error signal) through AMPA upregulation and the feedback constraint (priors) through NMDA blockade. The impairment of NMDA function would limit the extent to which priors could exert their effect in explaining the mismatch that is carried by the upregulated AMPA signaling. This would lead to persistence of perceptual aberrations due in part to persistent AMPA signaling and in part to an attenuation of the constraining effect that priors would normally afford on perception (see also study by Powers et al[20]). Intriguingly, contrary to ketamine, LSD alters glutamatergic function but it does not impair NMDA signaling[23] and may actually enhance it.[152] Thus, LSD induces more visual hallucinations, a phenomenon that can be captured by circular inferences.[121]

Conclusion and Recommendations for Future Research

Overall, this report reviewed the applicability of multiscale approaches of hallucinations presenting the current available data for an E/I imbalance in these experiences. Bayesian inference frameworks were shown to be particularly efficient for integrating various degrees of understanding, from the molecular to anatomo-functional or behavioral levels. Because of a specific lack of empirical evidence, neurophysiological validation of computational approach is urgently needed, notably to identify the possible neural implementations of belief propagation in both hallucinations and unbiased perceptions.[153] Three main lines of recommendations emerged from the working group. First in terms of population studied, it would be particularly useful if future research could devote concerted efforts in exploring these hypotheses transdiagnostically, to adequately control for SCZ as an independent factor: eg, comparisons of nonclinical individuals with hallucinations against healthy controls (none of the participants have SCZ, and they only differ on the presence of AHs), or studies comparing SCZ participants with and without AHs (all the groups have a SCZ diagnosis, but still only differ on AH). Beyond simple group comparisons, future cognitive studies could, for example, examine whether the magnitude of participant's DF or ICIM effect from different populations correlated with the number of intrusions they experience. This would notably allow to test whether intentional inhibition problems cause the intrusive cognitions reported in OCD and PTSD. Second, in terms of paradigms, multiscale approaches should be privileged, eg, combining cognition with MRS. Some specific recommendations could notably be made regarding emerging exploratory methods, like MRS. Indeed, GABA measures from the same brain regions as are targeted for measures of Glu could allow to sort out the specificity of E/I interactions for the initiation and maintenance of hallucinations. The validation of these experimental data through computational model fitting, based on predictive coding and circular inference frameworks, should finally reinforce the biological plausibility of the computational approach. This area of research is still in the early stages of development, but has the potential to make real improvement in our understanding of neurochemical causes of hallucinations and to optimized interventions.

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