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REVIEWS

Review

Disruption of Conscious Access in Schizophrenia

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Schizophrenia is a severe and complex psychiatric disorder resulting in delusions, hallucinations, and cognitive impairments. Across a variety of paradigms, an elevated threshold for conscious perception has been repeatedly observed in persons with schizophrenia. Remarkably, even subtle measures of subliminal processing appear to be preserved. We argue here that the dissociation between impaired conscious access and intact unconscious processing may be due to a specific disruption of top-down attentional amplification. This proposal is compatible with the neurophysiological disturbances observed in schizophrenia, including dysconnectivity, abnormal neural oscillations, and glutamatergic and cholinergic dysregulation. Therefore, placing impaired conscious access as a central feature of schizophrenia can help researchers develop a coherent and parsimonious pathophysiological framework of the disease.

A Neuroscientific Approach to Consciousness in Schizophrenia

Schizophrenia (see Glossary) is a severe disease that affects approximately 0.6–1% of the general population around the world [1]. Since the first descriptions of schizophrenia [2,3] it has been observed that patients are unaware of their symptoms, disconnected from reality, and exhibit negative symptoms that affect both high-level and basic cognitive functions. However, only more recently has it become clear that patients with schizophrenia exhibit specific deficits in conscious processing that could underpin most of these symptoms. Although consciousness has long been an important research topic in psychology and philosophy, its definition has been operationalized with the rise of cognitive neuroscience [4]: information is considered conscious if subjects are able to report it. By experimentally manipulating whether information is presented consciously or unconsciously to participants, neuroscientists have been able to compare how the two different information types are processed and to identify the neurophysiological signatures of consciousness [5,6].

Capitalizing on this growing science of consciousness, here we review recent results showing that persons with schizophrenia exhibit a dissociated profile of impaired conscious access and preserved unconscious processing. We discuss the plausible mechanisms of such a dissociation in light of the **global neuronal workspace** (GNW) theory of consciousness and disentangle the role of bottom-up and top-down deficits in this specific disruption of conscious access. We then confront those experimental results with recently proposed Bayesian models of schizophrenia. Finally, in line with the GNW model and the pivotal role of glutamatergic and cholinergic transmissions in conscious access, we examine the neurophysiological and molecular mechanisms that may underlie the dissociation between impaired conscious access and preserved unconscious processing in schizophrenia.

Trends

Patients with schizophrenia exhibit impairments of conscious processing and an elevated threshold for conscious perception, while subliminal processing is preserved.

The sensory impairments in schizophrenia could be explained by a disorder of conscious top-down attentional amplification rather than by bottom-up processing deficits.

Bayesian models account for the emergence of delusions through inappropriate updating of conscious representations according to sensory evidence.

Brain-imaging and neurophysiological studies of schizophrenia reveal anomalies in long-distance connectivity and synchrony between distant brain areas that may have a pivotal role in the disruption of conscious access.

NMDA receptors may have an important role in the pathophysiology of schizophrenia: there is growing evidence that NMDA receptors are dysregulated in this affection, that they have a prominent role in long-distance top-down connectivity, and that their disruption may induce psychosis and disorders of consciousness in subjects without schizophrenia.

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Dissociations between Conscious Access and Unconscious Processing in Schizophrenia

Explicit versus Implicit Behavior

Many high-level cognitive functions, such as memory, attention, processing speed and executive functions, are broadly impaired in schizophrenia. It was proposed that, in some domains, schizophrenia specifically affects explicit cognitive processing, while implicit abilities remain preserved [7–9]. Indeed, persons with schizophrenia were found to exhibit a selective deficit in explicit recollection, but no impairment in implicit memory as measured by familiarity [7]. Implicit grammar learning was also preserved [8]. Patients also showed preserved implicit emotion processing while they were impaired in explicit emotion classification [10,11].

Conscious versus Subliminal Processing

The dissociation between explicit and implicit processing has been further explored by comparing conscious versus **subliminal** processing. Studies of visual masking revealed an elevated threshold for conscious perception in schizophrenia [12–18]. For instance, when a digit was presented for a fixed duration and then, after a variable delay, followed by a mask made of several letters, persons with schizophrenia needed a longer delay than controls to consciously perceive the digit (Figure 1A,B). Similarly, patients are less likely to report that they perceive an unexpected event during **inattentional blindness** [19] and showed an exaggerated attentional blink effect compared to controls, associated with a decreased P300 [20]. Patients' nonaffected first-degree relatives may also exhibit an elevated masking threshold, suggesting that this finding is independent of medication and is an endophenotype of schizophrenia [21].

Remarkably, however, patients appear to process subliminal stimuli normally, resulting in a dissociation between impaired conscious processing and preserved subliminal processing. For instance, in number processing, conscious visual masking is impaired in schizophrenia while subliminal **priming** is preserved [14] (Figure 1C). Controls and patients were asked to compare a target number to five. This number was preceded by a fast presentation of another number that served as a prime and could be rendered invisible by masking. In the control group, performance in comparing the target number to five was affected by the congruency between the prime and the target under conscious (i.e., unmasked) and subliminal (masked) conditions: subjects were faster to answer when the prime and the target were congruent (both more or both less than five) than when they were incongruent (one more than and the other less than). However, in the patient group, the priming effect was observed only with subliminal primes but not with visible primes (Figure 1C).

Normal subliminal processing in patients with schizophrenia has also been observed in studies involving inhibitory processing [22] and emotional face or gaze direction processing under **continuous flash suppression** [23,24]. Some studies even suggest that masked emotional priming [25] and unconscious semantic priming [26] are enhanced in patients compared with healthy controls. Similarly, in a **change blindness** paradigm, patients moved their eyes toward the changes faster than did controls, suggesting normal or even enhanced unconscious processing, while their capacity to explicitly detect and report the changes was reduced [27]. Indeed, in the same studies, as soon as the threshold for conscious perception was crossed, conscious processing was impaired in schizophrenia, including inhibitory processing [22], number comparison [15], conscious priming [15], and conflict detection [14,28].

Impaired Metacognition and Conscious Error Detection

Metacognition, the ability to represent and monitor one's own mental state, is also subject to this dissociation between altered conscious processing and preserved unconscious processing. For instance, a recent study assessed conscious and unconscious error monitoring, using subjective reports and an electrophysiological measure of error detection, in controls and

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persons with schizophrenia while they performed a number comparison task on masked stimuli [13]. Persons with schizophrenia presented a decreased ability to monitor their own errors on conscious trials, accompanied by a severely reduced **error-related negativity** (ERN), as also reported in other studies (Figure 2A,B) [28,29] (reviewed in [30]). Remarkably, however, the patients' performance in unconsciously evaluating the likelihood of having made an error was preserved on masked trials (Figure 2D). This study also showed that the ERN was present exclusively on trials when subjects reported seeing the target number: when the same stimulus was presented at threshold, an ERN was seen only on seen trials, not on unseen trials (Figure 2D) [13]. Thus, this study demonstrates that schizophrenia affects conscious error detection, while leaving subliminal error monitoring essentially intact.

Self-Monitoring and Sense of Agency

In the phenomenological approach to perception, schizophrenia is described as a disorder of the sense of self, in which aspects of oneself are experienced as akin to external objects, with a weakened sense of existing as a vital and self-coinciding source of awareness and action (reviewed in [31]). Indeed, rigorous experiments have revealed deficits in conscious self-monitoring and agency. Persons with schizophrenia are impaired in discriminating their own hand from an alien hand [32]. Delusions of control can be conceptualized as a deficient representation of the links between conscious intention and action [33]. In a recent study [34], participants' sense of agency over subsequent action outcomes was manipulated by subliminal priming. Persons with schizophrenia showed a normal influence of subliminal priming on motor performance, but a reduced or even reversed influence of subliminal primes on the sense of agency, suggesting a dissociation between actual motor performance and the subjective feeling of control over action outcomes. This result again fits with the idea that, while automatic motor operations appear to be preserved, conscious aspects of motor behavior, such as sense of agency, are affected in schizophrenia.

A Framework for Anomalies of Consciousness in Schizophrenia

The Global Neuronal Workspace Theory of Consciousness

The above review shows that many cognitive impairments are demonstrated in schizophrenia. We posit that most, if not all, of them reflect a disruption in the ability to consciously access and manipulate information, with preserved unconscious processing. The GNW theory provides a theoretical framework that may account for this dissociation in schizophrenia. In turn, schizophrenia is a clinical condition that might be considered as a model disease to study which mechanisms are specific to conscious processing.

According to GNW theory [4,35–38], derived from Baars' seminal theory [39], conscious access rests upon the transient stabilization of neuronal activity encoding a specific piece of information. This occurs in a network of high-level brain regions interconnected by long-range connections, with the prefrontal cortex (PFC) acting as a key node. Conscious access starts when top-down attention signals amplify a relevant piece of information. On conscious trials, a wave of self-sustaining activity reaches the PFC, where information is stabilized and broadcasted to other areas. Global broadcasting is thought to render the information accessible to introspection and reportable to others (Figure 3). During access to a specific piece of information, other surrounding workspace neurons are inhibited and unavailable for processing other stimuli which remain **preconscious**, thus resulting in the attentional blink and other similar dual-task limitations. The transient dedication of central cognitive resources to a given stimulus is subjectively experienced as conscious perception [4,35–38].

Experimental tests of GNW theory have confirmed that a late and sudden nonlinear transition toward a metastable state of globally distributed brain activity, termed 'ignition', characterizes conscious access [40,41]. Whether a given stimulus will induce global ignition and, therefore,

Glossary

Aberrant salience: abnormal attribution of relevance to a stimulus that should normally be considered as neutral.

Attentional amplification: neurophysiological process through which a weak neural signal is strengthened by becoming the focus of attention, therefore increasing its chances of crossing the consciousness threshold.

Bayesian predictive-coding framework: theoretical model in which the brain continuously predicts upcoming events and uses Bayesian statistics to update posterior beliefs with sensory evidence to minimize prediction errors.

Beta-band: neural activity emitted in a frequency band between 13 and 30 Hz.

Change blindness: inability to detect a change in an image that flickers or changes very slowly.

Cholinergic neurons: nerve cells that use acetylcholine as a neurotransmitter. They are mostly located in the basal forebrain and are involved in wakefulness and rapid eye movement sleep.

Continuous flash suppression: psychophysical technique in which a stimulus is made invisible by being presented to one eye while other potent images are quickly flashed to the other eye.

Disorganization syndrome: incoherence between emotions, thoughts, and behavior, observed in persons with schizophrenia.

Error-related negativity: negative electroencephalographic component observed immediately after the subject makes an erroneous response.

Gamma-band: neural activity emitted in a frequency band between 30 Hz and approximately 100 Hz.

Global neuronal workspace (GNW): theoretical model according to which conscious access involves a large-scale neuronal network involving parietofrontal reverberant states and allowing the global sharing of information.

Ignition: sudden nonlinear transition toward a metastable state of globally distributed brain activity, characteristic of conscious access.

Inattentional blindness: inability to perceive an unexpected stimulus due to a lack of attention.

conscious perception, depends on both the initial amount of sensory evidence [40] and the availability of **attentional amplification** [41]. The GNW model predicts that two different mechanisms may affect conscious processing. At the sensory level, information may be too weak to be amplified. In this case, a bottom-up sensory deficit can lead to an elevated threshold of consciousness. Alternatively, sensory stimulation may be adequate but insufficiently amplified by top-down processes and/or maintained through self-sustained activity [42].

Bottom-Up versus Top-Down Impairment

Which of these mechanisms best explains the deficit of conscious access in schizophrenia? Based on neurophysiological data, several authors have defended the view that the elevated threshold for conscious access in schizophrenia arises from a low-level deficit (reviewed in [16]). The reasoning rests on the observation of anomalies in steady-state responses [43] and early ERPs, such as the auditory P50 in a variety of paradigms, including prepulse inhibition of startle responses by a weaker preceding tone, inhibitory gating in response to paired sensory stimuli, or mismatch negativity (MMN) [44,45] (reviewed in [46]). An anomalous visual P1 response to low spatial frequency stimuli is also present in schizophrenia and has been attributed to a specific bottom-up dysfunction of the **magnocellular visual pathway**, while the **parvocellular pathway** is preserved (reviewed in [47]). According to the bottom-up hypothesis, the increased visual masking in schizophrenia thus stems from this magnocellular dysfunction.

However, this bottom-up hypothesis was recently contested since there is no clear evidence for whether the magnocellular pathway is hyper or hypoactive in schizophrenia, which casts doubt upon its role in the elevated consciousness threshold observed in schizophrenia [17]. Moreover, perceptual visual deficits in schizophrenia could be related to impaired communication between dorsal and ventral visual pathways rather than to an impairment of a specific pathway [48]. A bottom-up impairment also appears to be incompatible with the full preservation of subtle measures of unconscious processing, such as subliminal priming [14,15]. Therefore, it was proposed that magnocellular channels contribute primarily to conscious object vision via a top-down modulation of re-entrant activity in the ventral object-recognition stream, and that the preserved unconscious priming involves intact parvocellular channels [49]. There is indeed ample evidence that, in healthy controls, information amplification depends on a combination of bottom-up and top-down factors, with attention and expectation having a major role [40,41,50–53]. Even early brain responses, such as the MMN [54,55], the visual P1 [56–58], or the auditory P50, in healthy controls [59] and persons with schizophrenia [60], are sensitive to attentional allocation and top-down signaling. For instance, a reduced MMN is observed in schizophrenia both when a surprising sound arises within a regular sequence and when a predicted sound is omitted, suggesting a top-down prediction impairment [61]. Moreover, most early processing impairments in schizophrenia are magnified under conditions of top-down amplification [18,62–65].

To provide a pure test of the existence of a bottom-up impairment in schizophrenia, differences between patients and controls should be re-examined under inattention conditions that minimize top-down amplification. A recent study [66] dissociated bottom-up and top-down components by flashing numbers at various levels of masking to healthy controls and to persons with schizophrenia, in two maximally different conditions: focused attention versus distraction by a difficult concurrent task. Under unattended conditions, ERP were indistinguishable between persons with schizophrenia and healthy controls. In particular, the amplitude of N1 and N2 events increased linearly with target-masked SOA, identically in both groups, suggesting that the linear accumulation of evidence, which constitutes the first stage of bottom-up processing of masked stimuli [40,67], was unimpaired. By contrast, a major impairment was observed in the focused-attention condition: the N1 component was insufficiently amplified, and the late nonlinear ignition component associated with the P3 component was drastically reduced (Figure 1D), consistent

Ketamine: noncompetitive NMDA receptor antagonist drug that is used as an anesthetic agent at high doses but can induce psychosis-like symptoms at lower doses.
Magnocellular visual pathway: dorsal visual stream that provides spatial, depth, and motion information.
Mismatch negativity (MMN): event-related potential elicited when the brain detects a violation in an established pattern of sensory input.
NMDA receptors: glutamatergic receptors activated by the neurotransmitter glutamate. They are thought to be involved in the formation of slow attractor states and in synaptic plasticity, learning, and memory.
Ongoing spontaneous activity: brain activity that unfolds in the absence of sensory input (i.e., during resting state).
Parvocellular pathway: ventral visual stream that provides identity, detail, or color information.
Phase synchrony: systematic temporal relation between oscillatory neuronal responses.
Preconscious: information that remains unconscious due to a lack of top-down attention, possibly due to distraction by a concurrent task.
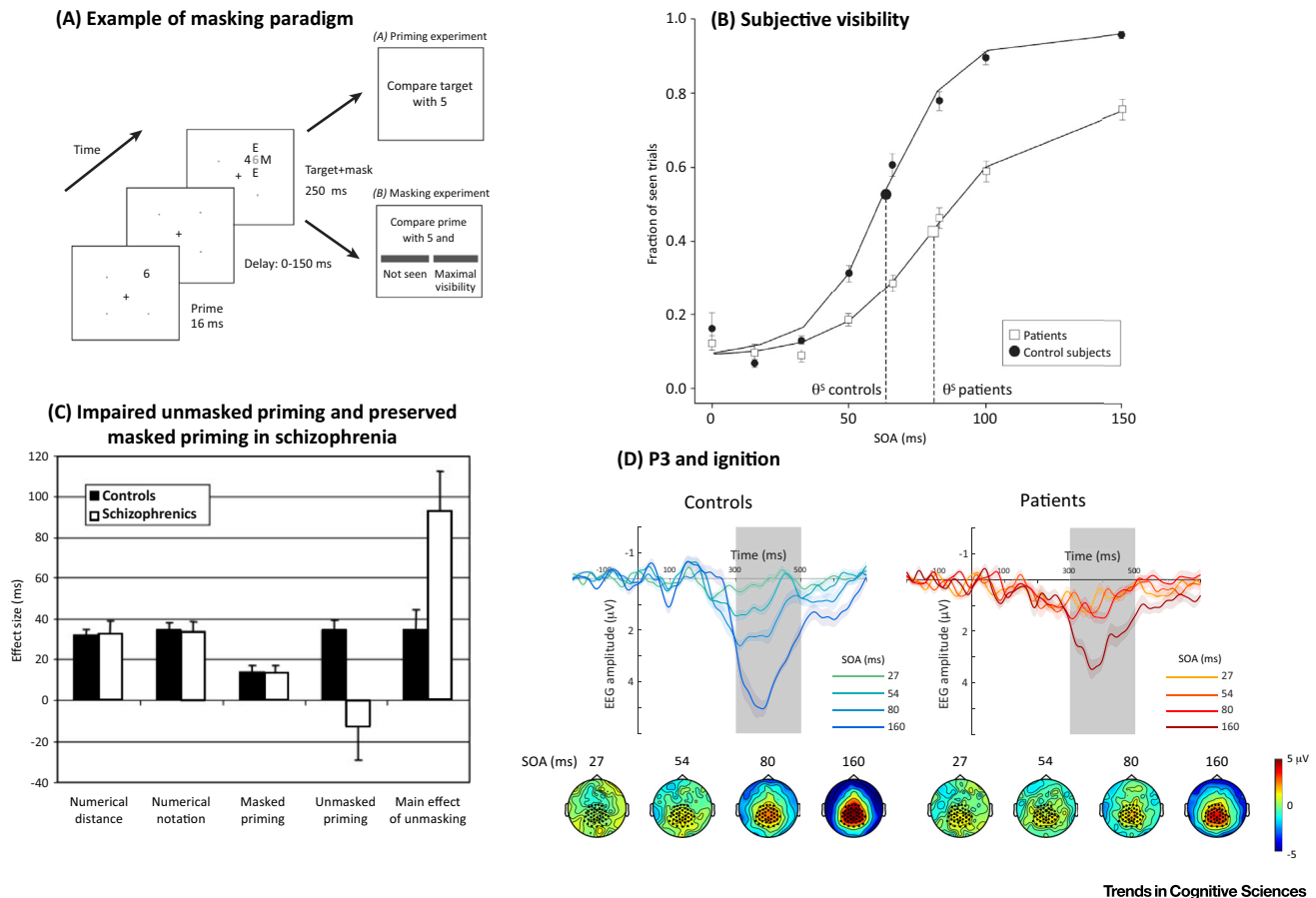**Prediction error:** difference between the actual outcome and the predicted outcome.
Priming: modulation of task performance on a stimulus due to pre-exposure to a related stimulus.
Prior: probability distribution representing a belief before it is updated by sensory evidence.
Schizophrenia: psychiatric disease characterized by positive symptoms, such as delusions (firmly held beliefs despite contradictory evidence) and hallucinations (perception without object), as well as negative symptoms, including withdrawal from social interactions and daily life activities, cognitive impairments, and disorganization syndrome.
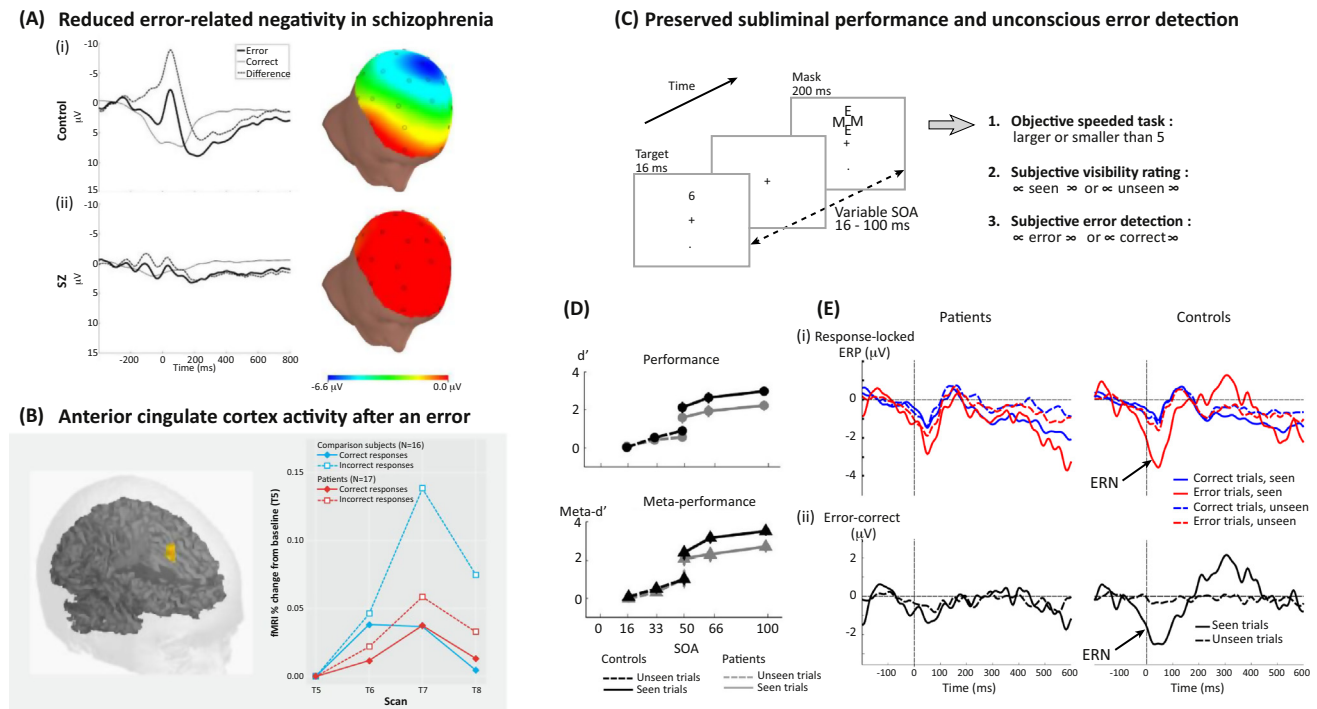**Subliminal:** information that is too short or too weak to be consciously perceived.

Figure 1. Conscious Access Is Impaired in Schizophrenia. (A) Example of masking paradigm by which conscious access can be parametrically manipulated. A digit (called the prime) is flashed for 16 ms. After a variable delay, it is surrounded by a mask comprising three letters and a target digit. The longer the delay between the prime and the mask (SOA), the higher the probability of seeing the prime. Participants can be asked various tasks: compare the target with five (priming), compare the prime with five (objective visibility), or report whether they saw it, using seen/not-seen labels or a continuous scale (subjective visibility). (B) Elevated subjective consciousness threshold in schizophrenia. Proportion of trials subjectively rated as 'seen' as a function of SOA. Subjective consciousness thresholds (θs) are defined in each group as the SOA for which the sigmoid curve reached its inflexion point. Error bars represent the standard error. (C) Both groups showed identical effects of numerical distance, number notation, and subliminal priming. However, they differed in the unmasked priming effect, which requires conscious control of interference. Patients were also severely slowed in the unmasked condition compared with the masked condition. (D) P300 and ignition are reduced in schizophrenia. Time courses of event-related potentials (ERPs) in P300 electrodes as a function of SOAs. Topographies show cerebral activity during the P300 time window. The cluster of electrodes is represented by the black dots in the topographies and the P300 time window by the gray rectangle in the time courses. Reproduced from [14,15,66].

with previous results [13,20,68,69]. Interestingly, patients showed an essentially normal attentional amplification of the P1 and N2 components, suggesting that only some but not all top-down attentional amplification processes are impaired in schizophrenia.

In summary, the time course of stimulus processing, as assessed by electrophysiological measures, suggests that most subliminal and preconscious stimuli are processed normally in schizophrenia. However, some stimuli that would have been conscious in healthy controls fail to cross the threshold for conscious perception and, thus, remain preconscious in patients with schizophrenia due to either a failure of top-down amplification or an inappropriately biased top-down amplification originating from the GNW (Figure 3).

Relation to Bayesian Models of Top-Down Predictive Coding
In the **Bayesian predictive-coding framework**, perception is considered a statistical inference that combines bottom-up incoming sensory evidence with top-down predictions based

Figure 2. Dissociation between Preserved Unconscious Confidence and Impaired Conscious Error Detection in Schizophrenia. (A) Error-related negativity (ERN) for control participants (i) and participants with schizophrenia (ii) during an arrow flankers task. Waveforms show channel Cz, and head maps show the difference between error and correct trials from 0 to 100 ms. (B) Persons with schizophrenia had a reduced error-related activity in the anterior cingulate cortex compared with normal subjects while performing a continuous performance task [press a target button whenever an 'A' (cue) was followed by an 'X' (probe), otherwise press another nontarget button]. (C) Experimental paradigm exploring error detection on seen and unseen trials. (D) Performance (d', circles) corresponds to the participants' ability to compare the target digit with five. Meta-performance (meta-d', triangles) corresponds to the subjective ability to determine whether this comparison performance was correct or erroneous. Patients (gray lines) and controls (black lines) exhibit identical above-chance performance for unseen trials (broken line) but not for seen trials (solid line). Thus, unconscious metacognition is preserved while conscious error detection is impaired. (E) Time courses of ERPs as a function of objective performance and visibility for controls and patients. (i) Grand-average ERPs recorded from a cluster of central electrodes (FC1, FC2, C1, Cz, and C2) for patients (left) no ERN is observed between erroneous (red lines) and correct (blue lines) trials, whereas a strong ERN is observed for controls (right). (ii) Difference waveforms for error minus correct trials show a strong ERN only for controls and only on seen (solid lines), not on unseen (broken lines) trials. Reproduced from [13,28,29].

on learned or innate **priors** [70]. In case of a mismatch, a **prediction error** signal is sent in the bottom-up direction to update the internal model and, therefore, minimize later surprise. This framework was recognized early on as having the potential to explain psychotic symptoms: hallucinations could be understood as an imbalance between priors and sensory inputs, whereas delusion would result from a failure to update beliefs according to incoming prediction-error signals [71,72].

Empirical data have provided support for the general notion of impaired inference in schizophrenia, making the world less predictable, more bizarre, and prone to delusions [73,74]. For instance, in a task of perceiving black-and-white Mooney pictures, a shift toward prior knowledge was observed in a clinical group of individuals with early psychosis, and was associated with proneness towards psychosis in the general population [75]. Conversely, many studies suggest that patients' perception is sometimes excessively biased toward sensory inputs. Patients can be remarkably less susceptible than control subjects to visual illusions that arise from a strong effect of prior knowledge on sensory interpretation [76]. Moreover, they have a weaker tendency towards perceptual stabilization during intermittent viewing of ambiguous stimuli [77] and are impaired in tracking predicted target trajectories during a smooth pursuit of
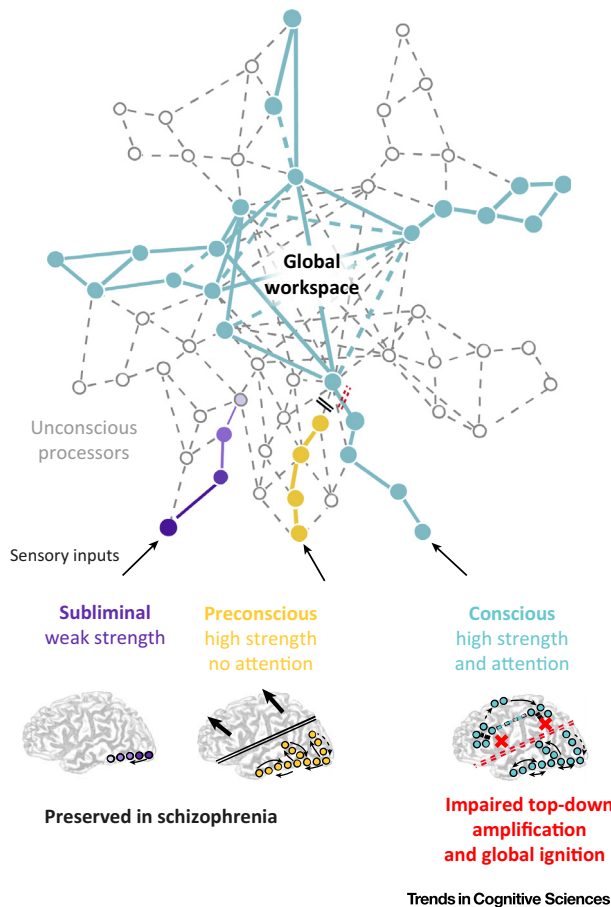
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Figure 3. A Hypothesis of Impaired Top-Down Amplification and Conscious Access in Schizophrenia. Dehaene *et al.* [37] distinguished three forms of processing in relation to conscious experience (i) subliminal processing, where incoming information is too weak to enter the global neuronal workspace (GNW) even if attended (purple color); (ii) preconscious processing, where information fails to be amplified by top-down attention and, therefore, is blocked from entering the GNW (yellow); and (iii) conscious processing, where information enters the GNW thanks to its strength and top-down amplification (light blue). Both subliminal and preconscious information are unconscious (i.e., not subjectively perceived and not reportable). Persons with schizophrenia show preserved subliminal [13–15,22] and preconscious processing [27], while conscious processing and conscious access are impaired [13–15,22]. In accordance with GNW theory, we postulate that the main mechanism of this impairment is an abnormal top-down amplification, which precludes information from crossing the threshold for access to consciousness. Thus, information that would have been consciously perceived by a normal subject remains preconscious, resulting in an elevated consciousness threshold.

occluded visual targets, but are better than controls in following unpredicted target deviations, suggesting that their perceptual predictions have reduced precision [78].

A related but distinct theoretical proposal builds upon the hypothesis of a disrupted balance of excitation and inhibition at the cellular level. It was suggested that, in psychosis, this imbalance brings forth a pathological form of causal inference called 'circular belief propagation' [79]. Instead of precisely cancelling each other through a perfect match, bottom-up sensory information and top-down predictions would reverberate and, thus, prior beliefs would be misinterpreted as sensory observations, and vice versa. Experimental evidence [80] suggests that schizophrenia is associated with an overestimation of sensory evidence through ascending inference loops, leading the patients to overestimated sensory evidence by erroneously combining it with itself and the prior multiple times: the patients 'expect what they see'. In a computational model used to fit patients' behavior, the free parameter that characterizes

these excessive ascending loops correlated with positive symptoms, while another parameter allowing for increased descending loops ('see what you expect') correlated with negative symptoms. Finally, both circular loops jointly predict a clinical measure of thought disorganization [80].

While these Bayesian models are built on a hierarchical view of brain function, they typically do not consider the specific role that conscious access may have in this hierarchy. The present review leads to the suggestion that bottom-up unconscious evidence accumulation is preserved or even enhanced in schizophrenia [27,78], and that the Bayesian inference deficit arises at the moment where conscious conclusions are drawn, through a discrete, sudden, nonlinear sampling of the unconscious distributions computed by unconscious processors [3]. The reduced GNW ignition, associated with a reduced P3 event-related potential, would then be a direct reflection of the failure to update conscious beliefs according to incoming evidence, as postulated by Bayesian theories.

Going further, the increase in the consciousness threshold and the presence of false inferences may mutually reinforce each other in schizophrenia. On the one hand, since expectations are known to facilitate conscious access [50,52,53], any impairment in the ability to draw inferences and to use them to develop expectations would result in an increase in the consciousness threshold. On the other hand, the gap between conscious representations and unconsciously processed incoming stimuli could give rise to inadequate inferences and, therefore, contribute to the **disorganization syndrome** observed in schizophrenia. Patients may not be able to consciously explain the aspects of their behavior, emotions, or intuitions that arise implicitly, guided by unconscious processing, and that occasionally burst into consciousness. Such unstable experiences would promote the invention of fictive interpretations and delusional beliefs, as also observed in patients with split-brains [81]. This hypothesis is in line with the phenomenological approach, which conceptualizes dysfunctions in schizophrenia as a deficit in the ability to combine components of self-experience into a coherent narrative [82].

Using computational modeling, it was recently demonstrated that, in an unstable environment, confidence is lowered. This leads to a reduction in the speed of reinforcement learning parameters, a metacognitive mechanism that is specifically disrupted in a **ketamine** model of psychosis [83]. Those effects are underpinned by altered neural activity in a frontoparietal network, including dorsomedial PFC and dorsal anterior cingulate. Interestingly, electrical stimulation of the dorsal anterior cingulate in humans elicits the subjective expectation of an imminent challenge coupled with a determined attitude to overcome it [84]. Dorsal anterior cingulate cortex is known to be activated during conflict monitoring [85]. Experiments indicate that overloading subjects with conflicting information induces a feeling of lack of control and leads normal subjects to endorse conspiracy theories or superstitions [86]. Therefore, we speculate that a similar effect may trigger, in persons with schizophrenia, the urge to search for an explanation and, thus, ultimately forge delusional beliefs.

Neurophysiological and Molecular Basis of Impaired Consciousness in Schizophrenia

Can the proposed dissociation shed light on the physiopathology of schizophrenia? The GNW model makes precise predictions about the neurophysiological impairments that may disrupt conscious access without impacting on unconscious processing. Since conscious broadcasting relies on a fast interconnection of distant brain regions, dysconnectivity or abnormal interareal synchrony could specifically disrupt conscious processing. Moreover, considering the pivotal role of **NMDA receptor**-mediated glutamatergic transmission in top-down attentional amplification, an anomaly of this receptor pathway may also account for schizophrenia symptoms. In this section, we discuss both hypotheses in turn.

Evidence for Dysconnectivity and Abnormal Oscillations

A key hypothesis of GNW theory [35–38,88,89], which is also mentioned in other theories of consciousness [87], is that conscious processing relies on long-range connectivity and synchrony to broadcast information to distant cerebral areas [35–38,88,89]. **Phase synchrony** is considered a basic mechanism through which information can be integrated across neuronal populations at multiple timescales [90,91]. Empirically, conscious perception in healthy controls is characterized by an increase in distributed **gamma-band** activity [92–94] and long-range **beta-band** communication [88,89,95].
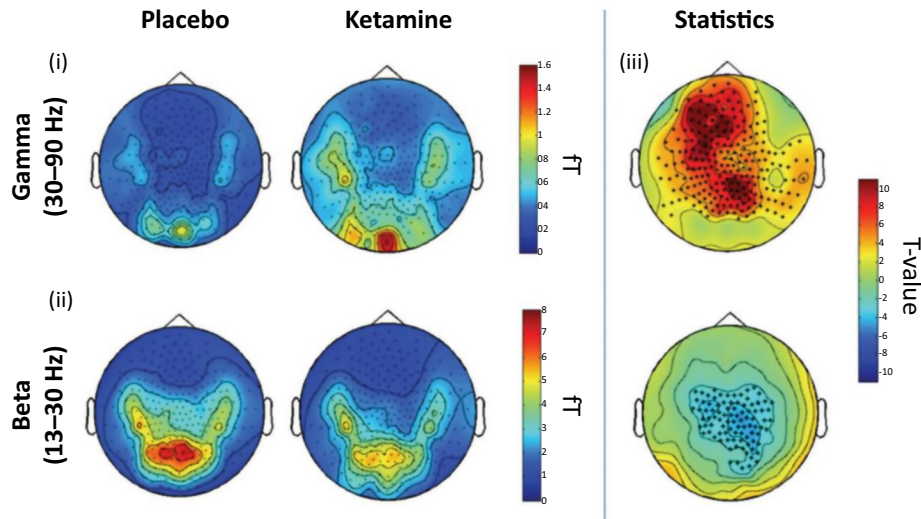
Therefore, it is of interest that these mechanisms appear to be strongly anomalous in patients with schizophrenia (Figure 4A), and could explain their disrupted conscious perception. The long-range synchrony of gamma and beta-band oscillations is disturbed in schizophrenia [96–98]. Persons with schizophrenia have long been known to exhibit abnormal anatomical and functional long-distance corticocortical connectivity (reviewed in [99]). Those findings fit with the dysconnectivity hypothesis, which postulates that the main symptoms of schizophrenia are better explained by abnormal connectivity and, therefore, impaired integration between distant brain regions [48,100,101] than by the isolated disruption of any localized brain process.

The NMDA Receptor Dysregulation Hypothesis

Early computer simulations of the GNW model hypothesized that bottom-up propagation is primarily supported by fast glutamatergic AMPA receptors, whereas top-down amplification is supported by slower glutamatergic NMDA receptors [36,102]. NMDA receptors are ubiquitous, but electrophysiological studies using NMDA receptor antagonists confirm that they are particularly involved in top-down signaling [103–106]. NMDA receptors also appear to be critical for attention-induced reductions in variance and noise correlations [103].

Remarkably, an abnormal regulation of NMDA receptors has been suggested to be the core pathology in schizophrenia [101,107–109]. Indeed, schizophrenia-like psychotic symptoms have been observed in patients with autoimmune anti-NMDA receptor encephalitis [110]. Similar symptoms can be induced in healthy controls by NMDA receptors antagonists, such as ketamine and phencyclidine [111–114]. It was demonstrated that subjects with remitted schizophrenia were sensitive to the psychotomimetic effects of infused ketamine and that it brought forward symptoms that were similar to their own symptoms [113], suggesting that glutamatergic hypofunction is close to the pathophysiology of psychotic symptoms in schizophrenia. The subtle alterations that are observed in schizophrenia, for instance in perceptual learning, reasoning, or in ERPs, such as the mismatch negativity, can also be mimicked in normal subjects by administration of low doses of ketamine [83,115,116]. At higher doses, ketamine induces anesthesia, probably when the disruption of long-distance prefrontal-parietal connectivity exceeds a threshold value [117]. Put simply, large-scale NMDA blockade can have a direct and massive impact on consciousness.

Therefore, a core dysfunction of NMDA-based corticocortical circuitry in schizophrenia appears as a plausible, although not necessarily unique, mechanism for the deficits in top-down attention, conscious access, and conscious processing. Such an hypothesis fits with the finding that NMDA receptor antagonists affect gamma-band activity and reduce alpha- and beta-band activity thought to be involved in long-distance communication and the mediation of feedback to lower sensory areas (Figure 4B) [103,118–121]. Depressed delta and theta frequency range power is also observed after administration of NMDA antagonists in nonhuman mammals and linked to a reduction in top-down connectivity [103,104]. In addition to disrupting brain rhythms, NMDA blockade could disturb conscious access by disorganizing neural assemblies through a decreased signal:noise ratio [122]. For instance, low-dose ketamine administration can be associated with an enhanced functional connectivity in healthy

(A) Long-distance phase synchrony is impaired in schizophrenia

(B) Ketamine increases gamma- and decreases beta-band activity

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Figure 4. Abnormal Neural Oscillations in Schizophrenia (ScZ) and under Ketamine Could Result in Impaired Conscious Access and Conscious Processing. (A) Mooney faces were presented in an upright and inverted orientation and participants indicated whether a face was perceived. (i) The average phase synchrony (indicated by the colored scale) over time for all electrodes. In patients with schizophrenia, phase synchrony between 200 ms and 300 ms was significantly reduced relative to controls. In addition, patients with schizophrenia showed a desynchronization in the gamma band (30–55 Hz) in the 200–280 ms interval. (ii) Differences in the topography of phase synchrony in the 20–30 Hz frequency range between groups. Red lines indicate reduced synchrony between two electrodes in patients with schizophrenia compared to controls. Green lines indicate greater synchrony for patients with schizophrenia. (B) Topographic plots represent the average power spectra (fT) of gamma (i) and beta (ii) frequency ranges recorded during the resting state by magnetoencephalography (MEG) after administration of placebo (left) or ketamine (right). (iii) Results of the nonparametric cluster-based statistic highlighting sensors showing a statistically significant effect for gamma (i) and beta (ii) frequencies (red ketamine > placebo; blue: placebo > ketamine) (*$P < 0.001$). Abbreviation: SD, standard deviation. Reproduced from [98,119].

controls [123–125]. In particular, a PFC hyperconnectivity correlating with the psychotomimetic effects was observed after ketamine administration in healthy volunteers. This effect mimicked similar observations in individuals at high risk for schizophrenia as well as in patients with recently diagnosed schizophrenia, but not in patients with chronic schizophrenia [123]. Such increased connectivity could result in a consciousness impairment either by fractioning the GNW into overactive subparts or by saturating the GNW with endogenous spontaneous activity and, therefore, preventing external stimuli from entering its bottleneck [126]. In the first case, rapid transitions between spontaneously activated GNW states could result in a disorganization syndrome [127] and hallucinations [128]. The second hypothesis, saturation, would be similar to what can be observed during the loss of consciousness in temporal lobe seizures, in which an excessive synchronization overloads the brain networks involved in conscious processing [129]. In both hypotheses, a few signals would be abnormally amplified, and would block conscious access to others, resulting in the subjective feeling that these amplified signals are particularly salient [130].

Other Molecular Alterations

NMDA receptor alterations are by no means the only molecular markers of schizophrenia. Psychotic symptoms could also result from anomalies in ɣ-aminobutyric acid-mediated (GABAergic), dopaminergic, and cholinergic circuits, which are frequently reported and which may interact with each other. Note, however, that an NMDA receptor dysfunction could be linked to such impairments [131]. For instance, reduced prefrontal NMDA input to the ventral tegmental area has two consequences: (i) reduce the activity of GABAergic interneurons in ventral tegmental area, which in turn increases or disinhibits the activity of dopaminergic cells projecting to the striatum via D2 receptors resulting in aberrant dopamine bursts; or (ii) decrease the activity of dopaminergic neurons projecting back to the PFC via D1 receptors [101,132,133]. In turn, dopamine bursts could reinforce the abnormal coupling of cortical networks resulting from NMDA receptor dysfunction, similarly to the demonstration of an increased cortical coupling in proportion to striatal prediction errors in healthy controls [134].

Serotonin and acetylcholine also act as potent modulators of NMDA-dependent cortical circuits, such that their dysregulation may disrupt NMDA receptor conductance properties, trafficking or subunit composition [101]. Indeed, the MMN and P50 suppression and dysconnectivity observed in persons with schizophrenia or in healthy controls after ketamine administration may be reversed by nicotine administration [135,136] (reviewed in [46]).

Crucially, serotonin and acetylcholine are also involved in the transition between the awake and asleep states. **Cholinergic neurons** contribute to cortical arousal and increase their firing prior to awakening through nicotinic and muscarinic effects in both thalamus and cortex [137]. Moreover, the cholinergic system has a crucial role in regulating **ongoing spontaneous activity**, in particular the generation of ultraslow fluctuations (<0.1 Hz) and their synchronicity [138]. Remarkably, a single-nucleotide polymorphism on the gene encoding nicotinic acetylcholine receptor subunit alpha-5 increases the probability of schizophrenia in humans and leads to impaired prefrontal-dependent behaviors and ultraslow activity, which can be rescued by nicotine administration [139].

Simulations of the GNW and experimental results indicate that low levels of arousal and vigilance (e.g., during sleep or vegetative state) can prevent conscious access [102,140,141]: the removal of a brainstem drive to GNW neurons may lead to a failure of global ignition by external stimuli, even if they are long and intense. A moderate level of spontaneous activity is needed to facilitate conscious access, particularly for weak stimuli, because it brings GNW neurons closer to firing threshold. Conversely, simulations also show that exceedingly high spontaneous activity, by inducing spontaneous endogenous ignition of

GNW neurons irrespective of external stimulation, has a blocking role and prevents access to other external stimuli [102]. Thus, consciousness deficits could arise from both upwards and downwards shifts in the level of spontaneous neuronal activity.

Concluding Remarks

Persons with schizophrenia exhibit an elevated consciousness threshold. In this paper, we argue that this anomaly is mostly due to attentional top-down deficits rather than to bottom-up impairments, since no deficit is observed under subliminal or inattention conditions. At a functional level, the disruption of consciousness appears to be underpinned by dysconnectivity among higher cortical areas participating in the GNW, a condition that can be triggered by impairments to NMDA-receptor mediated pathways and possibly to other systems such as cholinergic circuits.

Our proposal is that the conscious–unconscious dissociation is a fundamental distinction that must be taken into account to understand the core symptoms of psychosis. According to the present view, delusions constitute a set of conscious beliefs that remain stable even when they are contradicted by sensory evidence correctly processed at a lower subliminal level. The ensuing prediction errors, in turn, fuel a ceaseless search for these inadequate conscious explanations that we call delusions. This framework raises novel questions for Bayesian models of psychosis (see Outstanding Questions), and calls more generally for the use of experimental paradigms that dissociate cognition below and above the conscious threshold in schizophrenia. It also promotes interventions that would attempt to restore connectivity or synchrony in the GNW, possibly through glutamatergic or cholinergic modulation or brain stimulation.

Disclaimer Statement

Acknowledgments

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