REVIEW ARTICLE

Neural and neuronal discoordination in schizophrenia: From ensembles through networks to symptoms

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Abstract

Despite the substantial knowledge accumulated by past research, the exact mechanisms of the pathogenesis of schizophrenia and causal treatments still remain unclear. Deficits of cognition and information processing in schizophrenia are today often viewed as the primary and core symptoms of this devastating disorder. These deficits likely result from disruptions in the coordination of neuronal and neural activity. The aim of this review is to bring together convergent evidence of discoordinated brain circuits in schizophrenia at multiple levels of resolution, ranging from principal cells and interneurons, neuronal ensembles and local circuits, to large-scale brain networks. We show how these aberrations could underlie deficits in cognitive control and other higher order cognitive-behavioural functions. Converging evidence from both animal models and patients with schizophrenia is presented in an effort to gain insight into common features of deficits in the brain information processing in this disorder, marked by disruption of several neurotransmitter and signalling systems and severe behavioural outcomes.

KEYWORDS
fMRI, GABA interneurons, humans, oscillations, psychosis, rats

1 | INTRODUCTION

Schizophrenia is a complex neuropsychiatric disorder characterized by hallucinations and delusions, social withdrawal, restricted or inappropriate emotional expression and disorganized speech and behaviour.[1] Complex cognitive deficits are considered a stable characteristic of the illness[2] affecting a broad range of cognitive abilities including attention, processing speed and working memory, spatial and verbal memory, reasoning, planning, cognitive flexibility and

social cognition.[3] Cognitive dysfunction is present in most patients with schizophrenia. This dysfunction often precedes the clinical manifestation by years, persists during remission phases, predicts functional outcome and can be found in an attenuated form in first-degree relatives in cases of the familial type of the disorder.[4,5] Impaired cognitive control has been proposed as a core cognitive deficit in schizophrenia.[6,7]

Cognitive control is a higher order cognitive process[8] described as "the overarching ability to maintain the context for appropriate behaviour in a given situation in the face of interference".[6] According to the Research Domain Criteria (RDoC) Matrix[9] created by the National Institute of Mental Health, USA, cognitive control consists of goal selection, its representation, maintenance and updating, response selection, response inhibition and performance monitoring. Cognitive control, supported by the prefrontal cortex (PFC) and related to working memory,[9-12] manifests as the ability to use task-relevant cues and to ignore irrelevant or misleading stimuli.[13,14] However, as context and the environment inevitably change, selected goals and responses need to change accordingly to support adaptive behaviour. Cognitive flexibility[15] is the ability to adjust current goals and behavioural strategies in order to respond adaptively to altered environment. The hippocampus (HPC) is essential in representing contextual information,[16] and HPC-PFC interactions support flexible behaviour. A large body of evidence, some of which is discussed in later sections, shows that patients with schizophrenia display deficits in all of the above-mentioned cognitive abilities. Executive deficits in tests based on resolving conflicts between different sensory inputs/contexts or switching between alternative response strategies are hallmark cognitive symptoms of schizophrenia and strong predictors of occupational disability.[5,17-21]

A necessary prerequisite for cognitive functions is the coordination of neuronal activity across different timescales. The discoordination hypothesis of schizophrenia posits that diverse signs and symptoms result from the spatiotemporal disorganization of neuronal activity within and between groups of functionally related neurons (ensembles), while the response properties of individual neurons are mostly preserved.[22-27] By "neural coordination," we refer to the coordination of neural activity in large-scale networks as explored by functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and scalp electroencephalograph (EEG) studies. By "neuronal coordination," we refer to the level of microcircuits, local field potentials (LFP), neuronal ensembles and cell-to-cell interactions. The neural and neuronal levels of discoordination are linked by aberrant synaptic plasticity, arising from hypofunctional N-methyl-D-aspartate subtype of glutamate receptors (NMDAR)-mediated signalling, altered inhibitory, mainly gamma-aminobutyric acid (GABA) and neuromodulatory neurotransmission (dopamine, serotonin, acetylcholine), dysregulated excitation/ inhibition balance and maladaptive synchronization of neuronal discharge. In addition, deficiencies in white matter tracts and the myelination of interneurons and principal neurons might also contribute to the neural discoordination in schizophrenia.[28-31] The discoordination framework resembles the dysconnection hypothesis, put forth by Friston and colleagues, proposing that aberrant neuromodulation of NMDAR-related plasticity leads to alterations in functional connectivity and a failure of integration, which then acts as a proximal neurobiological cause of schizophrenia symptoms.[32-35] The discoordination framework emphasizes the intermediate level of neuronal ensembles.[23]

The causes of schizophrenia lie in both genetic and environmental factors interacting over the course of neurodevelopment and gradually progressing to the first outbreak of acute psychosis, which typically occurs when the patient reaches the early 20s. This process is captured by the "developmental risk factor model of psychosis".[36,37] The role of dopamine dysregulation in psychosis has been explored at length by other authors.[38-40] Although genetics, environmental factors and neurodevelopment play crucial roles in the causality of schizophrenia,[36] the focus of this article is to explore the neurophysiology of discoordination in patients and animal models from neurons, ensembles and local circuits to large-scale-networks and cognitive-behavioural manifestations, with aberrant neuroplasticity linking the explanatory levels.

2 | DISCOORDINATION IN NEURONAL ENSEMBLES

2.1 | Discoordination hypothesis is based on ensemble coding

The discoordination hypothesis is rooted in an ensemble coding perspective of neuronal network function. The idea that neuronal discharge is organized and coordinated across groups of neurons—neuronal ensembles—and that such organized discharge is the key mechanism of processing information in the brain have been present at least since Donald Hebb's work.[41] According to this view, neurons forming a cell assembly discharge together or in close succession, and their collective activation forms the neural substrate for the encoding of a mental object, a mental representation or an idea. In contrast, the dedicated coding scheme supposes that individual cardinal cells signal higher order concepts such as specific people (eg, Halle Berry) or significant events (11 September 2001).[42,43] Compared to dedicated coding by cardinal units, ensemble coding allows many more items to be remembered within a network with higher redundancy and robustness. It also permits pattern separation, pattern completion and linking different items in memory via a partial overlap between ensembles.[44] The activity of different ensembles needs to be
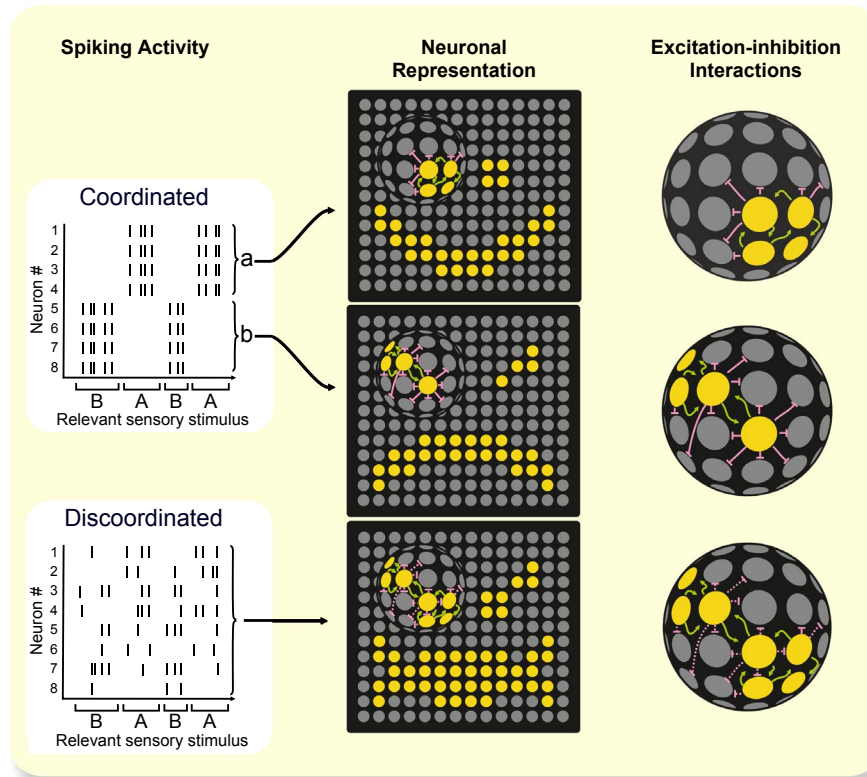
FIGURE 1 Hypothesized discoordination of cell assemblies on a timescale of tens to hundreds of milliseconds. Spiking activity top: Cartoon spike raster plot of 10 neurons organized in time into 2 ensembles. Lower-case "a" and "b" letters mark 2 distinct ensembles. Upper-case "A" and "B" mark relevant sensory stimulus at a given time. Cells forming a single assembly are concurrently active, cells participating in distinct assemblies do not discharge action potentials together. Spiking activity bottom: Raster plot of activity of the same set of 10 neurons when activity is discoordinated. Activation of neurons participating in different assemblies is not reliably separated in time. Neuronal representation top and middle: Cartoons of 2 distinct ensembles representing faces with distinct expression. Ensemble coherence is maintained by mutual excitation (green) between participating neurons. Activation of competing assemblies is suppressed by inhibition (pink) mediated by GABAergic interneurons (for simplicity interneurons are not shown). Neuronal representation bottom: Overlap of the 2 assemblies under the discoordination conditions leads to a loss of information. Impaired and suppressed inhibitory activity (marked by dotted pink lines) results in discoordination, impaired segregation of competing assemblies and a loss of information because of superposition catastrophe. Excitation-Inhibition interactions: enlarged depiction of neuronal representation with neuronal interactions. For experimental support see works by Fenton and Kelemen[52,54]

organized in time to prevent their simultaneous activation, which would lead to the superposition catastrophe, interference and subsequent information loss[14,23,45-47] as illustrated in Figure 1. These concepts were further developed along with accumulating anatomical and physiological data, and modelling work supports the view that the precise timing of neuronal spikes in neuronal ensembles is crucial for transmitting and processing information in the nervous system.[48] Impairment of this coordination both within specific neuronal circuits and between different brain regions of large neural networks may result in deficient cognitive control and behavioural disorganization.

Electrophysiological recordings of neuronal activity performed mostly in rodents demonstrate the importance of temporal coordination in neuronal firing; evidence for cell assemblies was reported in the hippocampus (HPC)[49] and the precise and reproducible temporal organization of ensemble discharge was observed in the visual cortex.[50] Furthermore, information encoded by distinct ensembles of co-activated neurons can be decoded in controlled experimental conditions. Different neuronal populations in the rodent HPC encode the position of the animal in dissociated spatial reference frames.[51-55] Similarly distinct temporally organized neuronal groups in the visual cortex encode distinct objects in the visual field.[56]

2.2 | Neuronal discoordination is present in animal models of schizophrenia

According to the discoordination hypothesis of schizophrenia, the disorganization of finely tuned neuronal discharge between groups of neurons is the underlying cause of disorganization on both cognitive and behavioural levels.[25,26] In this view, it is not the basic response properties of neurons that are affected but rather the temporal organization of their firing. That is, single neurons' responses to visual, spatial and other type of stimuli remain intact, but

the coordination of firing between neurons and ensembles is impaired.

Indeed, altered organization of neuronal discharge was observed in models of psychosis and schizophrenia in rats. Dizocilpine (MK-801), an NMDAR antagonist with psychotomimetic effects, causes the disorganization of temporal discharge of HPC CA1 neurons, so that pairs of neurons that discharged at separate times prior to drug exposure start firing together.[57] This disorganized state, marked by a selective increase in co-activity between previously non-coactive neurons (hypersynchrony), was also observed in the HPC CA1 and medial PFC (mPFC) after the administration of another NMDAR antagonist phencyclidine (PCP).[58] In agreement with the discoordination hypothesis, neuronal discoordination induced by NMDAR antagonists was observed without major effects on firing rate in anaesthetized animals[57] or the spatial response properties of neurons in freely moving rats.[58] In addition to pharmacological models based on NMDAR antagonists, unilateral HPC inactivation by the voltage-dependent Na^+ channel blocker tetrodotoxin (TTX) also impairs cognitive control in rats and increases coactivity in the uninjected HPC.[59]

Hamm and colleagues[60] used viral transgenic expression of a fluorescent Ca^{2+} indicator to compare population activity patterns in the rodent visual cortex after chronic ketamine and in a genetic mouse model ($Df^{A+/-}$) of schizophrenia susceptibility. In a striking, parallel to the effect of other NMDAR antagonists (MK-801, PCP) on immediate-early gene expression[61] and on electrophysiological neuronal activity in anaesthetized[57,59] as well as in awake rats,[58] cortical ensemble activity patterns were less distinct and their (re-)activation was less reliable in both the chronic ketamine and $Df^{A+/-}$ genetic model.[60] In other words, different ensembles were less distinct and similar ensembles were less similar. Figure 2 (Ensemble overlap) depicts alterations in ensemble similarity.

The observed increase in coactivation of originally non-coactive neurons could severely compromise the network's ability to form and maintain distinct ensembles representing
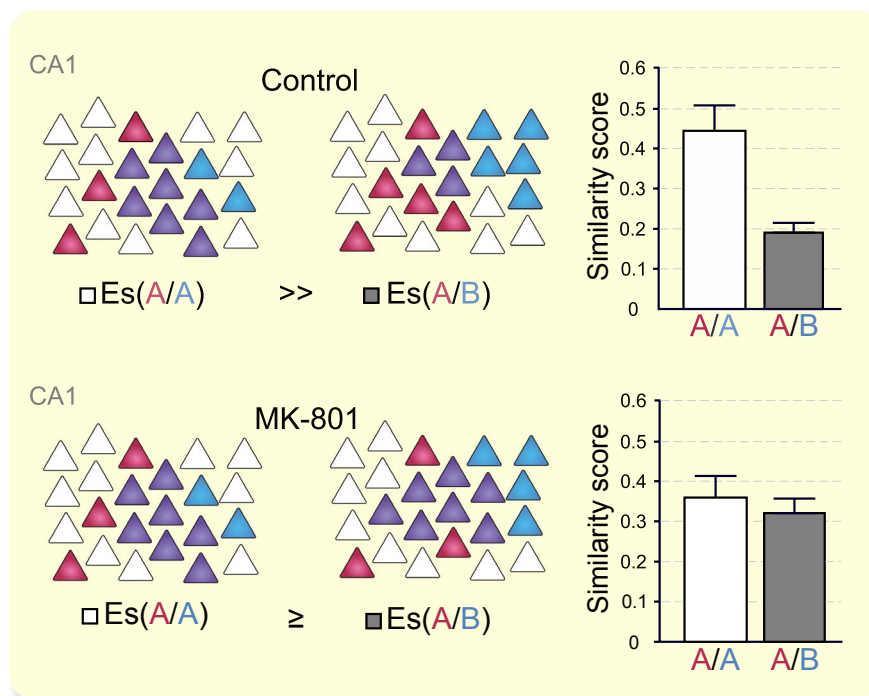

FIGURE 2 Discoordination of plasticity-related activity in a MK-801 schizophrenia model using 2 -time point immediate-early gene imaging *Arc/Homer1a* catFISH. Animals received two 5 minutes exploratory sessions separated by 20-minutes rest in home cages. Some animals explored the same environment twice (A/A), others explored 2 distinct environments (A/B). Neurons active during the first exploratory episode are marked pink (*Homer1a+*), neurons active during the second episode are depicted blue (*Arc+*). Neurons that were active in both episodes are marked purple (*Arc/Homer1a+*) and signify the similarity of the 2 representations. Top *Normal*: The ensemble similarity (Es) is far greater in the same conditions (A/A) than in different conditions (A/B) in controls, so that Es (A/A) >> Es (A/B). Bottom *Schz*: In an MK-801 animal model of psychosis, the Es (A/A) is reduced (less reliable reactivation) and Es (A/B) is increased (loss of distinctiveness) so that Es (A/A) ≥ Es (A/B). Right: Bar graphs (adapted from Kubik et al[61]) showing the Similarity Score of ensembles active during the 2 time periods. Group A/A explored the same environment twice, group A/B explored 2 different environments. Cage control animals that did not explore any novel environment had SS close to zero (not depicted). Zero SS means no above-chance coactivation (overlap) of plastically active neurons during the 2 episodes, while a full above-chance overlap would be marked as 1. Error bars display SEM. Bar graphs adapted from Kubik et al.[61] For details see works by Guzowski, Vazdarjanova and Kubik[61-63]

separate, context-specific classes of information. The impaired categorization of stimulus representation could account for the failure of cognitive control (distinguishing relevant from irrelevant) that has been observed in animal models.[23,59,61] Neuronal ensembles in a hypersynchronous network will tend to merge into unreal representations giving rise to excessive and inappropriate neuronal associations. Their consolidation by maladaptive synaptic plasticity may promote the consolidation of aberrant connections leading to delusions, hallucinations and thought disorder.[58,64] Spurious associations in speech samples have been found in patients with schizophrenia, their first-degree relatives with high risk of developing the illness, and individuals with schizotypy traits, suggesting that hyperassociation reflects an underlying susceptibility (hypersynchrony) and represents an endophenotype of schizophrenia.[65-67]

3 | THE GABAERGIC SYSTEM AND EXCITATION/INHIBITION DISBALANCE IN SCHIZOPHRENIA

3.1 | Interneurons organize neural activity

Alternations in inhibitory interneuron activity can directly affect the organization of activity on the ensemble level and potentially explain disorganization in neuronal discharge. Ensemble activity patterns are maintained by mutual excitation between the ensemble members and the inhibition of non-member neurons, leading to the activity having attractor-like organization.[68] It should be noted, however, that even in areas with little recurrent connectivity, ensemble properties may be "inherited" from upstream recurrent networks, such as in the CA1 region. Different cell assemblies alternate in their activation, reflecting the behavioural needs of the animal.[49,52,69] Altered inhibition within the network can lead to an impaired inhibition of firing of neurons outside the active assembly. This would manifest as the hypersynchrony observed by Szczurowska et al[57] and Kao,[58] and result in less stable, shallow attractor states.[68,70] Multiple classes of interneurons undoubtedly play different roles in the organization of network activity. This organization is an emergent property achieved via a complex of feedback, feedforward, lateral, homeostatic and higher order (dis)inhibitory interactions, in concert with excitatory and modulatory neurotransmission.

3.2 | Interneurons are essential in neural oscillations

Generally, interneurons can be divided into 3 non-overlapping classes based on the expression of either parvalbumin (PV), somatostatin (SST) or ionotropic serotonin receptor 5HT3a (reviewed in[71]). These main classes are further subdivided according to morphological types, other molecular markers or electrophysiological properties. The PV+ interneurons (PVIs) are fast-spiking (FS), and include basket cells (PVBCs) targeting proximal dendrites and the perisomatic area and chandelier cells (PVChCs) that synapse at the axon initial segment of pyramidal cells. In addition, PVBCs form chemical[72,73] and electrical synapses (gap junctions)[74-76] with other PVBCs. The 5HT3a class consists of VIP neurons that target SST+ interneurons and non-VIP interneurons electrically coupled to interneurons of other types. SST+ interneurons target dendrites of principal cells. Both SST and 5HT3a classes are non-fast spiking, showing spike frequency adaptation.

Firing of FS interneurons is robustly coupled to gamma rhythm.[77] Optogenetic manipulations have provided direct evidence of a causal relationship between fast-spiking PVIs and gamma oscillations. More specifically, optogenetic activation of PVIs selectively amplified gamma-band frequency,[78,79] while light-driven activation of pyramidal neurons amplified only oscillations at lower frequencies.[78] On the contrary, optogenetic inhibition of PVIs abolished gamma oscillations.[79]

Two general types of computational models describe mechanisms for the generation of gamma oscillations (reviewed in[80,81]): the interneuron network gamma (ING) models, also referred to as inhibitory-inhibitory (I-I) models, and the pyramidal-interneurons network gamma (PING) models, also referred to as excitatory-inhibitory (E-I) models.

In ING models, the gamma rhythm is first set in a network of inhibitory interneurons and only subsequently is transferred to the population of principal cells. Minimal requirements for the emergence of gamma oscillations in ING models[80] are: mutual inhibition between interneurons, a short-time constant of GABA$_A$Rs and excitatory drive provided to the interneuron network, which can either be tonic or stochastic.[81] Transfer of the rhythm from PVIs to PCs might occur via "post-inhibition excitation"—a phenomenon in which asynchronous spiking of pyramidal cells becomes synchronized after a transient period of strong inhibition.[82] The PVBCs display properties well suited for the implementation of ING models,[81] including mutual inhibitory connections,[72,73] fast GABA$_A$R-mediated IPSCs[83,84] and strong glutamatergic synapses with a high density of AMPARs receiving excitatory drive from principal cells.[82,85] Besides glutamatergic synapses, the PVBCs can also receive excitatory drive from other PVBCs via gap junctions.[74-76] In addition, GABAergic synapses between PVBCs are shunting rather than hyperpolarizing, meaning that the reversal potential of GABA$_A$-mediated synaptic current lies between the resting membrane potential and the action potential threshold.[86] The shunting synapses between PVBCs support homogenization of PVBC action potentials even with stochastic excitatory drive.[81,86]

In PING models, gamma rhythm emerges from the iterative interaction between excitatory and inhibitory neurons mediated by feedback inhibition. When the rhythm is stabilized,

the network alternates between phases of fast excitation and delayed feedback inhibition.[80] Therefore, in PING models, the spiking of principal cells and interneurons are shifted in phase relative to each other, with the degree of phase shift determining the frequency of the gamma rhythm.[80] The PING model predicts a delay between principal and inhibitory neuron discharge, consistent with observations made in vitro and in vivo.

3.3 | The GABAergic system is abnormal in schizophrenia

Considerable evidence supports the notion that the GABAergic system is abnormal in patients with schizophrenia. These include alterations in GAD67, parvalbumin, somatostatin, α1 and α2 GABA receptor subunits, GAT1 transporter and potassium channels.

A key enzyme in GABA synthesis is glutamic acid decarboxylase (GAD), occurring in 2 isoforms, GAD67 and GAD65. Although both isoforms are present in most interneuronal types, up to 85% of GABA is synthesized by GAD67.[87] One of the most replicated *post mortem* finding in patients with schizophrenia is the reduction of the GABA-synthesizing enzyme GAD67;[88-90] while GAD65 remains mostly unchanged.[91,92] More specifically, the density of GAD67+ neurons in patients is reduced, but the amount of GAD67 in neurons with detectable levels remains unchanged. This has been observed throughout the brain including neocortical regions, subcortical structures[88,93] and the HPC region.[94,95]

Reduction of parvalbumin is a widely replicated finding in patients with schizophrenia.[96-101] The density of PV+ cells is normal,[96,101] but the amount of parvalbumin in PV+ cells is lower in patients with schizophrenia.[97-100] Nonetheless, some studies have also found a reduced density of PV+ cells in the HPC area.[102,103] Dual GAD67/PV in situ labelling *post mortem* shows that only half of PV+ neurons contain detectable levels of GAD67,[99] suggesting that GAD67 is absent specifically in a subset of PVIs, possibly the PVBCs.[104]

Somatostatin levels in SST+ interneurons and the density of SST+ cells are substantially reduced in patients with schizophrenia.[102,105] Levels of GABA$_A$Rs with the α1 subunit are decreased at PVBC-PC synapses,[106] while levels of GABA$_A$Rs with the α2 subunit are elevated at PVChC-PC synapses.[107] The GABA membrane transporter GAT1 responsible for GABA-reuptake is decreased at the PVChC-PC synapse.[108,109] Interestingly, potassium Kv3.1 and Kv9.3 channels that support the fast-spiking properties of PVIs[110] are also affected in schizophrenia. Kv3.1 channels are reduced specifically in unmedicated patients, but not in patients treated with antipsychotics.[111] Kv9.3 channels are also reduced in patients with schizophrenia; however, chronic antipsychotic treatment in monkeys does not affect Kv9.3 levels.[112]

3.4 | Functional aspects of GABAergic abnormalities in neuronal networks

Next, we examine how GABAergic abnormalities are intertwined with neuronal and network activity. To this end, we chose the hallmark GABAergic abnormality present in patients with schizophrenia—the GAD67 reduction in PVI+ interneurons—as an exemplar. The aim of the following inquiry into GAD67 alterations is not to postulate the primacy of GAD67 in the pathophysiology of schizophrenia. Rather, it serves as a convenient well-researched constituent of the GABAergic system whose interaction with neuronal and network activity can be explored in some detail. Briefly, levels of GAD67 affect the inhibitory capacity of interneurons, thus influencing the E/I balance of the network. Conversely, levels of GAD67 itself are regulated by the activity of the network via excitation-transcription coupling. In the next section, we explore the relationship between network activity and GAD67 as an exemplar of GABAergic system alteration in more detail.

Generally, inquiries into the functional meaning of abnormality are aided by the notion of the "four Cs".[113] With regard to the disease process, a given abnormality might constitute a: (a) Cause, an upstream factor related to the disease pathogenesis; (b) Consequence, a deleterious effect of a cause; (c) Compensation, a response to either a cause or consequence that helps restore homeostasis; and (d) Confound, a product of factors frequently associated with, but not a part of, the disease process, or an artefact of the approach used to obtain the measure of interest.

Although the reduction of GAD67 varies substantially between individuals, it is not attributable to medication status, drug abuse, disease severity or measures of functional outcome.[91,114] Therefore, GAD67 reduction is most probably part of the pathophysiology of schizophrenia itself[104]—a possible cause, consequence or compensation, but not a confound.

3.5 | Cause—GAD67 reduction as a causal factor in schizophrenia

The most direct approach to test for a causal role of GAD67 in schizophrenia pathophysiology is by genetic ablation of the GAD67 gene *Gad1* and studying molecular, electrophysiological and behavioural phenotypes relevant to schizophrenia. In one study, removal of one allele of the GAD67 gene mostly in PVIs led to schizophrenia-related phenotypes.[115] In another study, haploinsufficiency in *Gad1* selective to PVIs in juvenile mice conferred deficient inhibitory synaptic transmission and pyramidal cell disinhibition.[116] However, synaptic transmission was restored to normal when mice reached adulthood.[116] The authors suggested a homeostatic response because of increased PVI feedback excitation being

responsible for this normalization.[116] In another model, deletion of the NR1 NMDAR subunit in approximately half of the cortical and HPC interneurons early postnatally induced a schizophrenia-like phenotype including GAD67 reduction.[117] Importantly, if the same NR1 deletion occurred only post-adolescence, no GAD67 deficit or schizophrenia-related phenotypes were observed.[117] Such a GAD67 reduction is also present in the developmental[118,119] and pharmacological models.[120] An epigenetic model based on prolonged subcutaneous L-methionine administration also induced a GAD67 deficit.[121] These genetic, developmental and pharmacological models utilize either manipulations during early development or sub-chronic NMDAR antagonist administration to induce schizophrenia-like phenotypes including GAD67 reductions. Disrupted neurodevelopment or prolonged drug application opens a temporal window in which downstream or compensatory changes might take place. This notion complicates the interpretation of GAD67 reduction as a clearly causative factor behind schizophrenia-like phenotypes. In addition, even if GAD67 reduction causally conveys a schizophrenia-like phenotype in animal models, this does not necessarily mean it has to be so in human patients.

3.6 | Consequence—GAD67 reduction as a downstream consequence of interneuron hypoactivity due to NMDAR hypofunction

Studies examining the activity of PVIs and the role of NMDARs in schizophrenia indicate that GAD67 reduction could be a downstream consequence or even a compensatory attempt at restoring the E/I balance. Similarly to a number of other proteins implicated in schizophrenia,[122] the expression of GAD67[123] is regulated by excitation-transcription (E-T) coupling, a process in which protein transcription is induced by the excitatory signals a given neuron receives.[124-126] Since PVIs are considered hypoactive in schizophrenia, it is reasonable to suspect that GAD67 reduction is a result of decreased PVI excitation. We briefly explore 3 models that account for a decrease in PVI activity in schizophrenia and therefore GAD67 reduction being either a consequence or compensation.

The first and widely influential model states that NMDARs located directly on PVIs are hypofunctional, causing decreased interneuron excitation with subsequent pyramidal cell disinhibition.[90,127-132] This could lead to GAD67 reduction (mediated by E-T coupling) as a downstream consequence of insufficient PVI activation. The disinhibition hypothesis is based on the paradoxical action of an NMDAR antagonist presumably acting preferentially on PVIs that leads to the increased excitation of pyramidal neurons.[129] In this context, the proposed location of hypofunctional NMDARs is the postsynaptic membrane of PVIs at the PC-PVI synapse. The specific subtype of PVIs suggested by most authors is the

PVBC. However, the view that hypofunctional NMDARs are located on PVBCs has been disputed on a number of lines.[133] One argument is that the role of NMDARs in driving PVBC activity is much smaller than in pyramidal cells.[134,135] In addition, a knock-out of NMDARs from PVIs induces schizophrenia-relevant deficits and sensitizes mice to the effects of the NMDAR antagonist MK-801.[136] However, an intriguing possibility compatible with both the modest role of NMDARs in driving PVBC activation and PVBC-located NMDAR hypofunction has recently been proposed. Originally discovered in the spinal cord, NMDARs located on the presynaptic terminals (preNMDARs) were found to facilitate the neurotransmitter release.[137] The role of NMDARs on PVBCs in GABA discharge has recently been tested directly by Pafundo and colleagues,[138] who used whole-cell recordings in synaptically connected PVBC-PC pairs from mice ex vivo PFC. After stimulation of preNMDARs, the authors observed a 40% enhancement of synaptic current at PVBC-PC pairs. The amount of GABA released was unchanged, but the probability of transmission failures decreased when preNMDARs were stimulated. The consequences of plausibly hypofunctional preNMDARs at the PVBC-PC synapse depend on the activity state of the network (see[138]). The reasoning is that preNMDARs at the PVBC-PC GABAergic synapse might be active only when network activity is high and glutamate is sufficiently elevated to reach a heterosynaptic connection.[138]

3.7 | Compensation—GAD67 reduction as compensation in response to insufficient excitation between principal cells

Abnormality does not necessarily imply pathology. The second model conceptualizes the decrease in PVI-activity as a compensatory mechanism in response to deficient excitation between pyramidal cells.[82,104,139] Reductions in dendritic spine density and dendritic arbours of pyramidal cells are well documented in patients with schizophrenia.[104,113] In support of this notion, the density of excitatory synapses onto PVIs in dlPFC is reduced in patients with schizophrenia, and this synapse reduction is predictive of decreases in GAD67 and PV expression.[140,141] Reductions in excitation between pyramidal cells could trigger multiple compensatory responses such as a decreased inhibitory activity of PVIs, including GAD67 reduction. The overall postulated effect would be a narrow E/I dynamic range.[104]

The third model, recently proposed by Nakazawa and colleagues,[142] fits to some extent between the 2 previous models by combining NMDAR hypofunction on both PVIs and pyramidal cells. The main idea is that NMDAR hypofunction occurs as 2 spatially and temporally distinct events over the course of development. The first NMDAR deficit occurs in PVIs in the early postnatal period, disrupting maturation of cortical circuits and increasing E/I. The increased excitation

elicits glutamate spillover in the prodromal period. Since hyperglutamatergia is excitotoxic, pyramidal cells respond to NMDAR over-activation by their homeostatic internalization, resulting in the second NMDAR hypofunction. The authors acknowledge that NMDAR hypofunction on GABAergic neurons in early development "remains highly speculative because there is no convincing evidence of reduced NMDAR-mediated glutamatergic neurotransmission onto PVIs in patients with schizophrenia",[142] p. 8). Incidentally, Chung and colleagues have provided such evidence.[141]

3.8 | Inhibitory and excitatory effects of GABA

Adult GABAergic interneurons are expected to exert inhibitory effects on their postsynaptic targets. However, excitatory GABAergic neurotransmission is observed during prenatal and early postnatal development.[143] At the level of neuronal networks, the functional meaning of GABAergic abnormality changes depending on if GABAergic synapses are inhibitory or excitatory. The direction and magnitude of chloride currents upon GABA-A receptor activation, and therefore the inhibitory or excitatory effects of GABA, depend on local concentrations of chloride ions across the plasma membrane. Two types of sodium/potassium-chloride co-transporters with opposite effects establish chloride gradients locally, namely NKCC1 (Cl- uptake) and KCC2 (Cl- extrusion). The switch from the excitatory to inhibitory effect of GABA during development is based on the rise of KCC2 expression, which begins at the end of the first postnatal week in rodents.[144] Interestingly, some evidence suggests that PVChCs might produce excitatory postsynaptic currents (EPSC) even in adulthood, ie, have depolarizing effects.[145] Locally reduced functional capacity of the KCC2 transporter at the postsynaptic membrane of the axon initial segment might constitute a plausible mechanism.[146] If indeed excitatory, the effects of PVChC on pyramidal cells might be especially pronounced in schizophrenia. An elevated NKCC1/KCC2 ratio, which resembles the immature pattern, was found in the PFC and HPC formation of patients with schizophrenia,[147] and a decrease in KCC2 was found in the dlPFC.[148] In another study, however, levels of both NKCC1 and KCC2 in the dlPFC of schizophrenia subjects was found to be normal.[149] NKCC1 and KCC2 are regulated by phosphorylation carried out by 2 kinases, OXSR1 (OSR1, oxidative stress responsive 1) and WNK3 (with-no-K-(lysine)-protein-kinase-3). Phosphorylation enhances the function of NKCC1 (more Cl- transported into the cell), but decreases the action of KCC2 (resulting in less Cl- extrusion from the cell), resulting in a local increase in chloride ions in the axon initial segment. Interestingly, OXSR1 and WNK3 kinases were found to be overexpressed in patients with schizophrenia.[149] Overexpression of α2-GABA-A receptors and a decrease in presynaptic GAT1 at the PVChC-PC synapse could be compensatory mechanisms aiming to strengthen GABAergic transmission. If PVChCs are indeed inhibitory, the disinhibition hypothesis prevails (although it would not explain the overexpression of OXSR1 and WNK3 kinases). On the other hand, excitatory PVChCs would support the hypothesis of insufficient excitation between pyramidal cells, with a homeostatic reduction of PVBC inhibition and an increase in excitation by PVChCs as compensatory mechanisms. The question of whether PVChCs have excitatory effects on principal cells in adult in vivo brain is not yet settled.[150,151]

3.9 | Conclusions on interneurons and discoordination in schizophrenia

To summarize, GABAergic interneurons are essential in organizing neuronal population activity and the emergence of neural oscillations. The presence of numerous abnormalities in the GABAergic system is well established in patients with schizophrenia. However, the functional contribution of these GABAergic abnormalities to the pathophysiology of schizophrenia and their effects on network dynamics remain to be determined.

4 | DISCOORDINATION IN THE HIPPOCAMPAL CIRCUIT

4.1 | Role of the hippocampus in disorganization symptoms

Cognitive and behavioural disorganization is typically measured as an executive deficit in the control of behavioural responses (selection and inhibition, selective attention, sustained attention and attentional set-shifting) and is functionally linked to the PFC. However, the HPC, traditionally associated with spatial navigation and memory, is also involved in resolving response conflicts.[152] The memory function of the HPC may support comparisons of actual sensory information with stored representations.[153] Interestingly, the predictive processing account of psychosis supposes that the primary deficit is because of aberrant prediction error signalling from these comparisons.[154] The HPC also supports context-dependent sensory discrimination and organizes representations into a succession of predictions and planned behaviours.[155-159] In patients, the disorganization manifests behaviourally as inappropriate ordering of tasks.[160] Overall, the disorganization in schizophrenia may arise from a compromised ability of the HPC to coordinate streams of sensory and memory information and to organize them into behaviourally adaptive sequences.

4.2 | Three hippocampal circuit models

Converging evidence points to disrupted processing along the HPC trisynaptic loop as a critical circuit deficit responsible for disorganized cognition.[14] We briefly explore 3 hippocampal models, namely the dentate gyrus (DG) hypofunction, the CA3-CA1 disconnection and the OLM/PVBC disbalance model.

Behavioural pattern separation, usually assayed as fine spatiotemporal discrimination, is typically attributed to competitive network properties of the dentate gyrus.[161-165] Dentate-selective dysfunction could promote hallucinations and delusions generated by the remaining HPC circuitry unconstrained by the discriminative role of the DG and enhanced by the increased negative emotional bias present in schizophrenia.[166] A hyperactive, hypersynchronous, and hyperplastic network in CA3 can account for the hyperassociation, impaired habituation and episodic memory, and the inability to use contextual information observed in patients with schizophrenia (Figure 3 Trisynaptic loop).

However, a similar functional deficit (reduced resolution manifesting on subtle differences) could also result from a disconnection downstream of the DG. If neurons in CA3 and CA1 cannot transmit the input from the DG, the resulting functional deficit may largely recapitulate the dentate-related impairments. A disorganization of HPC ensemble activity patterns paired with a loss of ensemble code for (spatial) context and impaired cognitive (spatial) coordination on a rotating arena (Carousel)[22,23,59] have been observed in CA1 of rats after the systemic NMDAR antagonists PCP[58] and MK-801.[57,61] Aberrant ensemble code for spatial context after systemic MK-801 was found in rat CA1, but not in CA3.[167] This uncoupling may reflect an altered balance between CA1 inputs in favour of the temporoammonic pathway and resulting reduced precision of memory of prior experience from CA3 relative to sensory input from EC. It is also possible that the uncoupling reflects circuit adaptation to aberrant activity in CA3, but the endpoint is largely the same (Figure 3B Trisynaptic loop).

Schizophrenia is associated with alterations of oscillatory patterns in population activity in multiple brain areas.[26,169] These oscillations provide "neural syntax" for meaningful processing of sequential neuronal ensemble activity and time windows for synaptic plasticity.[170] Inappropriate timing of spiking activity manifested as altered oscillations may give rise to corrupted ensemble code, maladaptive synaptic plasticity and schizophrenia symptoms.[64,171,172] In the hippocampus, input from CA3 is associated with the dominance of slow gamma (25-55 Hz) over fast gamma (60-100 Hz) oscillations and controls memory recollection.[173] In contrast, input from entorhinal cortex (EC) to CA1 is associated with fast gamma and carries information about current sensory experience for
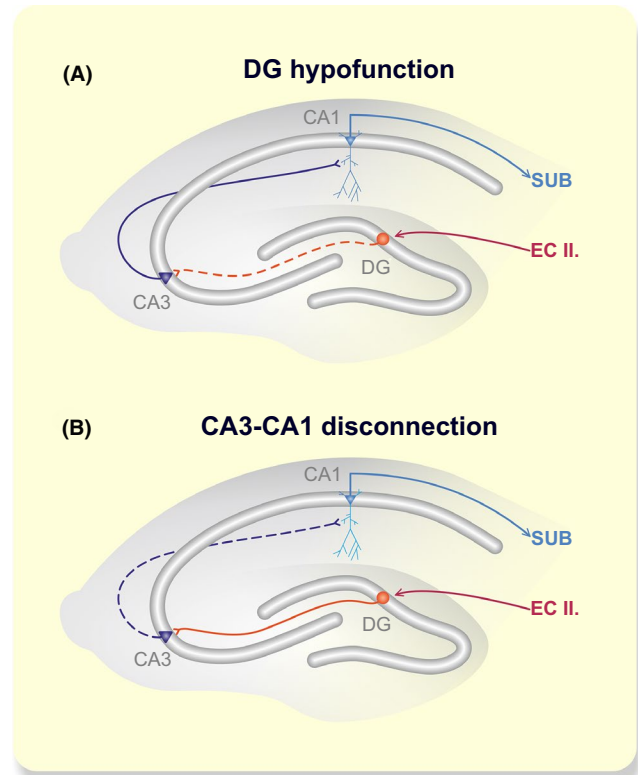

FIGURE 3 Trisynaptic loop models of impaired pattern separation in schizophrenia. A, DG hypofunction model: A dysfunctional dentate gyrus impairs pattern separation, CA3 is hyperactive (adapted from Tamminga et al[168]) B, CA3-CA1 disconnection model: Functional disconnection of CA3 and CA1 —as observed after systemic MK-801 by Buchtova et al[167]— may also manifest as impaired pattern separation. EC II, second layer of the entorhinal cortex; DG, dentate gyrus; SUB, subiculum

encoding.[174,175] Acute PCP administration in awake behaving rats increases the power of HPC fast-frequency gamma oscillations, which thus gains dominance over slow gamma.[58] Since fast frequency gamma coordinates CA1 activity with its major afferent input from the medial EC, this indicates a predominance of input from the EC at the expense of input from CA3.[176] As already mentioned, decreased communication (ie, uncoupling) between CA1 and CA3 subregions after MK-801 was also observed using immediate early gene expression.[167] These results point to an enhanced reliance of CA1 on the direct "sensory" cortical input and a suppressed processing of learned and stored information from the CA3. Additionally, an increase in fast-frequency gamma power was accompanied by increased theta modulation of fast gamma (theta-fast gamma coupling[58]). Discoordination between HPC theta rhythms in the 2 hemispheres has been observed in a developmental model of schizophrenia elicited by a neonatal ventral hippocampal lesion (NVHL), thus pointing to another level of neuronal disorganization.[177,178]
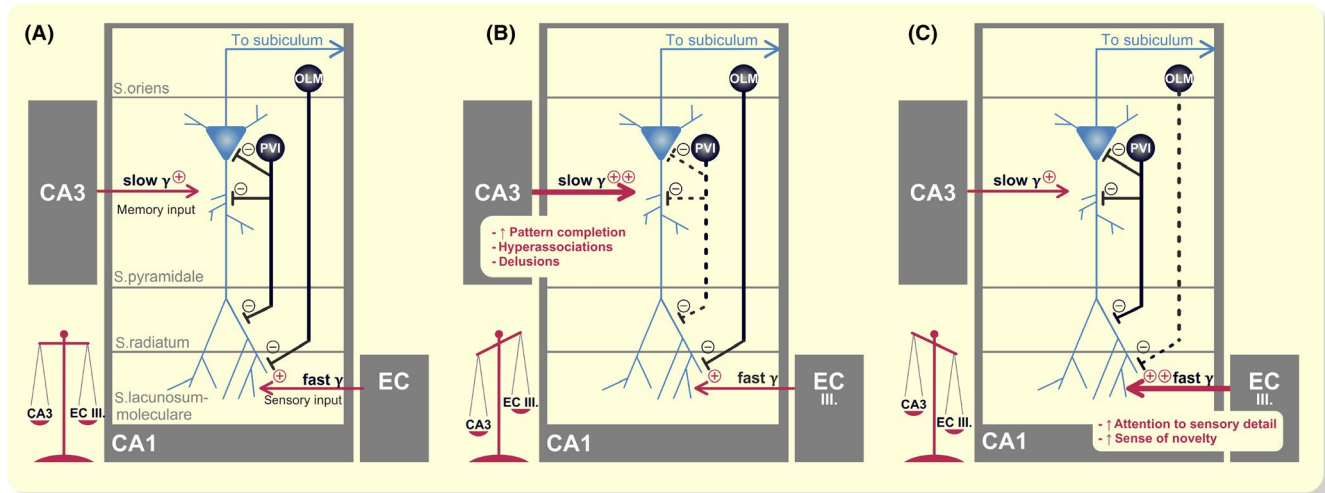
FIGURE 4 Hypothesized OLM/PVBC disbalance in CA1. Input from CA3 and EC to CA1 pyramidal neurons is layer specific; it is associated with slow (25-55 Hz) or fast (60-100 Hz) gamma oscillations and the weight of this input is modulated by PV+ interneurons (PVI) or OLM interneurons respectively. Both PVIs and OLM interneurons are abnormal in schizophrenia. A, Normal function: Both PVIs and OLM interneurons function properly, input from CA3 and EC to CA1 pyramidal neurons is in balance. B, PVI dysfunction: Dysfunction of PVIs enhances CA3 input to CA1, biases the system toward stored representations (increased "priors" in Bayesian terminology) and exaggerated pattern completion, possibly supporting hallucinations, hyperassociations and resistance of delusions to change. C, OLM interneuron dysfunction: Dysfunction of OLM interneurons enhances EC input to the CA1 region, and biases the system towards sensory information (increased "likelihood of data") manifested as increased attention to sensory detail, an increased sense of novelty, delusion formation, deficits in habituation and resistance to illusions. EC III, third layer of the entorhinal cortex; PVI, parvalbumin-positive interneuron; OLM, oriens lacunosum-moleculare interneuron. Image adapted from Heckers and Konradi 2015[179]

A third model, based on GABAergic interneuron abnormalities found in schizophrenia patients posits that the balance between CA3 and EC inputs to CA1 may sway either way (Figure 4 OLM/PVBC disbalance model). This is not necessarily in conflict with the above-mentioned predominance of EC-related input to the CA1 as observed in NMDAR antagonist animal models because acute administration of NMDAR antagonists mimics mainly acute psychosis.[120] In the CA1, specific subclasses of GABAergic interneurons regulate the relative strength of spatially segregated input pathways and therefore the weight of distinct information streams.[179] Input from CA3 targets the middle part of CA1 pyramidal cells' apical dendrites located in the stratum radiatum. The PVBC interneurons in CA1 target the perisomatic area of pyramidal neurons in the stratum pyramidale and stratum radiatum. Thus, the PVBCs inhibit information flow from CA3 and promote extrahippocampal input to CA1 from the EC. This input from EC targets the apical parts of CA1 pyramidal neuron dendrites located in the stratum lacunosum-moleculare. Interneurons in the stratum oriens, which target apical dendrites in the stratum lacunosum-moleculare (O-LM cells), suppress EC input to CA1 and favour information processing from CA3.[180]

These observations are suggestive of a disbalance between CA3 and EC information inputs to the CA1 region mediated by GABAergic interneuron dysfunction, possibly altering CA3/EC input weights in CA1. This may produce

2 opposing effects, namely either the memory aspect of CA3 or the more sensory-related EC input predominates in the CA1 region. Because both PVBCs and OLM interneurons gating the 2 information streams are abnormal in schizophrenia, both variants are possible. This may result in hyperassociation in the case of increased pattern completion if CA3 input predominates or an increased sense of novelty in previously encountered items because of minor alterations in the context if the EC input predominates. The latter may account for the habituation deficits and increased salience of sensory stimuli as observed in patients with schizophrenia. Phenomenologically, psychotic disorders are characterized by both exaggerated cognitive pattern completion resulting in delusions and by increased attention to sensory stimuli.[181]

These hippocampal models can also be understood in terms of Bayesian (non-conscious) inference and its neural implementation as specified by predictive coding. This approach represents a general framework of brain function applicable across explanatory levels, including single cells, neuronal ensembles and subjective experience. Briefly, expectations based on prior experience ("priors") are compared to actual sensory input ("data") in a hierarchical system.[182-184] Their difference weighted by their relative precisions (reliability) gives rise to "prediction errors," signals used to update the representation of prior experience in order to improve future predictions, thus giving rise

to "posterior probability," which may later act as a next "prior." Top-down are propagated priors, while bottom-up are propagated only prediction errors. Predicted signal is cancelled at a given level and not propagated further upwards. This framework explains psychotic symptoms in terms of an altered precision of priors and the likelihood of sensory data giving rise to the disrupted updating of priors.[154,185-187] In Bayesian terminology, the altered balance of CA3-EC input to CA1 can be conceptualized as the altered probability of priors (CA3 input) and likelihood of sensory data (EC input) resulting in aberrant prediction errors and posterior probability.

5 | DISCOORDINATION IN LARGE-SCALE NETWORKS

The discoordination of neural activity in schizophrenia has been described not only in terms of microcircuits but also on the level of large-scale networks. Based on functional brain imaging, disordered inter-regional functional connectivity has emerged as a key pathophysiological substrate of psychotic symptoms.[188] The notion that specific symptoms of schizophrenia arise from altered functional coupling between distinct brain regions is captured in the concept of disconnection.[32-35,189] Importantly, the disrupted functional connectivity (ie, dysconnectivity) may involve not only weakened pathways but also exaggerated connections, both resulting in altered neural integration and aberrant information processing.[33,35,190] First, we briefly review structural abnormalities that are documented in patients with schizophrenia, in both grey and white matter. Then we focus on altered functional connectivity, mainly concerning the so-called triple network and fronto-temporal connections. Afterwards we explore the effects of ketamine in both healthy volunteers and animals as a valuable translational tool in understanding functional connectivity of large-scale networks in schizophrenia.

5.1 | Morphological alterations and structural connectivity

Despite some variability in published findings, morphological alterations in both grey matter volume and white matter connectivity are well documented in schizophrenia.[191] These alterations may impact neuronal communication and integration in the affected frontal and temporal areas, functional connectivity between these regions, and be detrimental to cognitive functioning.

Reductions of grey matter volume in patients with schizophrenia are present in the medial and superior temporal cortex, PFC, insula and midline structures of the frontal lobe such as the anterior-cingulate cortex (ACC).[191] However,

these reductions do not reflect the loss of cell bodies, but rather diminished dendritic complexity and synaptic density.[113,192] Reductions of white matter, as reported by tractography studies (see meta-analysis by[193]), are present in regions of the frontal lobes (tracts interconnecting the frontal lobe, thalamus and cingulate gyrus) and temporal lobes (tracts interconnecting the frontal lobe, insula, HPC-amygdala, temporal and occipital lobe), suggesting impaired frontotemporal communication. However, our recent findings have suggested that the decreased integrity of white matter tracts in the whole white matter lacks specificity for brain lobes in schizophrenia.[194] These global or localized white matter changes in schizophrenia could be responsible for aberrant information transfer and functional discoordination between large-scale networks.

Dysfunction of the above-described frontal and temporal regions could explain the presence of cognitive deficits as observed in schizophrenia, since many cognitive functions are critically dependent on these areas and preserved communication between them. Importantly, structural changes reported in schizophrenia are in line with progression of the illness and the accompanying cognitive deficits. The grey matter volume reduction in the ACC and insula precedes the first psychotic symptoms, while transition to psychosis and further chronicity are associated with additional morphological changes in the adjacent regions of the mediofrontal cortex and the temporal lobe.[195] Considering the HPC, bilateral reductions in size have been reported not only in chronic and first-episode patients, but also their non-psychotic siblings, and individuals at high-risk of psychosis.[164] Moreover, basal perfusion, a proxy of metabolic activity, is increased in the medial temporal lobe of patients and to some extent is normalized by antipsychotics.[164] Longitudinal observations of clinical high-risk individuals suggest that hypermetabolism in the left anterior CA1 region precedes conversion to psychosis and subsequently leads to atrophy in the left anterior HPC.[196] Studies in mice corroborate this interpretation, as ketamine increases blood volume in the vHPC, corresponding to the anterior HPC in humans.[196] Both human[197] and animal[198,199] studies show that hyperactivity of the HPC can increase dopamine release in the striatal region, which may lead to aberrant salience and psychosis.[200]

Similar deterioration patterns can be observed in the neurocognitive impairment profile of patients with schizophrenia. First, only mild impairments of executive and attentional processes related to the frontal lobes (mainly in auditory working memory, processing speed and verbal learning) can be observed during the prodromal phase of the illness with progressive decline in working memory and processing speed in first-episode patients.[201,202] A further deterioration of cognitive functioning, especially in declarative (verbal and episodic) memory can be observed in the conversion to chronicity. This deficit of declarative

memory is associated with the length of the illness[203] and can be explained by additional morphological changes in medio-frontal and temporal areas. The observation that the above-reported alterations evolve over time[195,204,205] highlights the important role of neuronal plasticity in the course of the illness.[32,113]

5.2 | Functional connectivity

Given the fact that the above-reported brain regions implicated in schizophrenia represent important hubs of large-scale networks, reductions in both grey matter volume and white matter tracts may subserve neural discoordination at the macroscopic level. In the context of complex cognitive and behavioural deficits in schizophrenia, whole brain functional connectivity (FC) techniques[206] are of particular importance.

Data based on temporal coupling of fMRI signal from distinct brain areas during rest- (task-free) and stimulus-dependent (task-related) activations have led to the identification of large-scale brain networks, which are characterized by spatially consistent functional connectivity of intrinsic brain activity.[207] Although other networks such as the visual or sensorimotor may also be observed during whole-brain FC methods, 3 main large-scale brain networks have been identified: the default mode network (DMN), the central executive network (CEN) and the salience network (SN),[208] illustrated in Figure 5. It is widely accepted that coordination of these 3 brain networks plays a key regulatory role in organizing neural responses associated with cognitive functions and complex human behaviour.[208,209] Briefly, in humans, the CEN is anchored in the dlPFC and PPC (posterior parietal cortex) and is associated with executive functions during task-related paradigms. The DMN lies in the mPFC (including the orbitofrontal and anterior cingulate cortices), PCC (posterior cingulate cortex) and the HPC and is associated with internally oriented processes such as episodic memory recall or processing of contextual information. Lastly, the SN is rooted in the fronto-insular cortex and dACC (dorsal anterior cingulate cortex) associated with salience detection. Moreover, the SN includes subcortical and limbic structures that are involved in reward and motivation (VTA, substantia nigra).[210]

Homologs of the DMN[211,212] and probably the SN[213] are also present in rodents (reviewed in[214]). However, it is important to note that some candidate homological brain areas are subject to debate. Despite the fact that the cytoarchitectural features of the human PFC are hardly developed in rodents, the rodent mPFC is suggested to functionally correspond to the dlPFC in humans and non-human primates.[215-217] Indeed, connectional and neuropsychological evidence indicates the role of the rodent mPFC in executive functions (including working memory, cognitive flexibility, attentional set shift and strategy switching, the selection of appropriate rules and
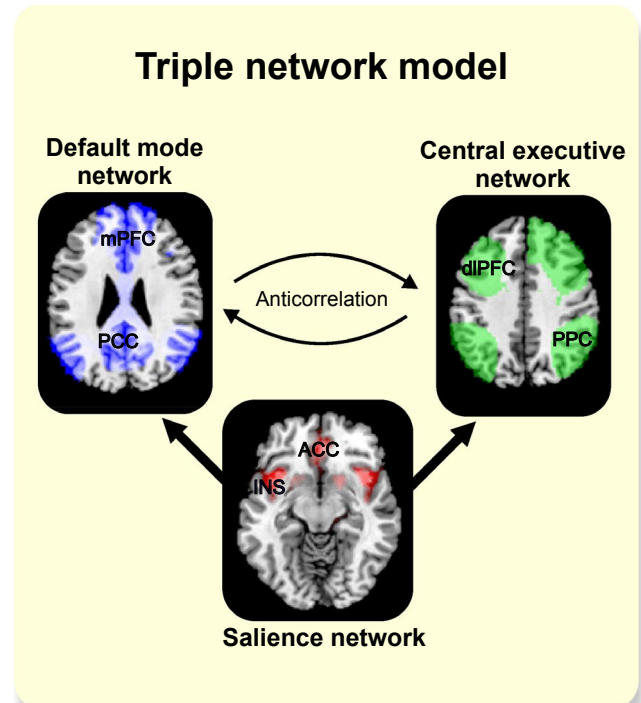

FIGURE 5 Schematic illustration of the triple network model consisting of the salience network (SN), default mode network (DMN), and central executive network (CEN). According to this model, the SN coordinates the CEN/DMN activity, ie, activates the CEN and deactivates the DMN in response to salient stimuli. ACC, anterior cingulated cortex; DPLFC, dorsolateral PFC; PPC, posterior parietal cortex; mPFC, medial PFC; PCC, posterior cingulate cortex; INS, anterior insula. Adapted from Menon and Uddin;[221] Sridharan et al[222] and Menon[209] (the images of networks derived from our in-house resting fMRI sample, n = 23)

the inhibition) strongly associated with human dlPFC and thus the CEN.[218-220] However, anatomical evidence supports the view that the rat mPFC is related to both the primate ACC and dlPFC (for review see[220]). Therefore, interpretations of comparative studies related to the PFC in rats and humans should be carefully considered.

Numerous resting-state and task-related fMRI measurements in patients with schizophrenia have repeatedly shown aberrant functional connectivity within and between DMN, SN and CEN, when compared to healthy subjects.[223-232] Generally, patients with schizophrenia display reduced anticorrelation (increased FC) between DMN and CEN. It has also been shown that deficits in cognitive tasks aimed at attention and working memory are correlated with hyperactivity of the DMN and increased connectivity within this network, suggesting a dysregulation of inhibitory brain circuits in schizophrenia.[233] The regulatory role has been assigned to the SN, which is thought to mediate switching between the DMN and CEN in the healthy brain, while altered SN/insular function[234] might be associated with the reduced anticorrelation of the DMN and CEN observed in patients with

schizophrenia.[208,209,221] Indeed, lesion and activation studies demonstrated that structural SN integrity and activation plays a crucial role in coordination of the other 2 major brain networks.[222,235]

This model is in line with the structural deviations consistently reported in schizophrenia that are located in deep frontal structures and the key hubs of the SN regions of the insula and ACC.[236-239] Moreover, as the SN is involved in the detection and processing of emotionally salient events,[240] altered salience and salience prediction error coding controlled by the insula[234,241] may specifically contribute to psychotic symptomatology.[234,242] It has been suggested that the assignment of aberrant "proximal salience" to internally generated mental events (inner speech, self-generated actions, etc.) contributes to altered self-monitoring, explaining the positive symptoms of hallucinations or passivity experiences.[234,242] Indeed, the weakened engagement of SN-related cortical midline structures along with a substantial attenuation of anti-correlated DMN/CEN activity were demonstrated in deficient self/other-agency discrimination in first-episode schizophrenia (FES) patients.[243] The model of impaired anti-correlated relationships between the task-positive CEN and task-negative DMN because of malfunctions in salience network areas may therefore represent a pathophysiologically relevant phenotype of schizophrenia,[209] linked to the self and theory of mind dysfunctions along with complex cognitive deficit,[244] negative symptoms and positive symptoms such as auditory verbal hallucinations[227] and delusions of reference.[208] The aberrant triple network activity may also be explained in the context of high-frequency attractor states of neural networks,[68] where both insufficient suppression (impaired inhibition) of noise generated by the DMN during task performance and a decrease of auto-excitation of the CEN contribute to positive symptoms in schizophrenia.[245] Thus, real events might be perceived as dream-like experiences on the one hand, while on the other hand, the noise-generated false percepts might manifest as clear, consciously experienced delusions or hallucinations.

Congruently, a recent resting fMRI study showed reduced, less persistent and more variable dynamic SN-centred cross-network interactions in patients compared with control subjects, and these dynamic measures were correlated with positive (but not negative) symptoms. These interaction patterns used as factors in multivariate classification analysis distinguished patients from control subjects, with accuracy of almost 80%.[246]

Although the medial temporal lobe is generally considered to be an accessory hub of the DMN,[208,247] the addition of the left HPC as a fourth component to the triple network model was suggested by Lefebvre[248] in order to more fully explain network dynamics at individual stages of hallucinations. A study testing this quadripartite model[248] showed that periods with hallucinations were linked to memory-based sensory input from the HPC to the SN, while the extinction of hallucinatory experience was associated with takeover of the CEN in favour of voluntary processes. Although the role of the HPC in schizophrenia is evident (see morphological changes and discoordination of the HPC microcircuit), it is possible that the suggested quadripartite model could arise simply from altered dynamics between frontal and temporal brain areas reported in schizophrenia.

5.3 | Fronto-temporal interactions in schizophrenia

Fronto-temporal interactions have been extensively investigated in patients and to some degree also in animal models of schizophrenia. In humans, the HPC, residing in the temporal lobe, is part of the task-free DMN, while the dlPFC belongs to the task-positive CEN. Thus, to support optimal performance during cognitively demanding paradigms, these 2 regions should be anticorrelated in their activity. Indeed, in healthy controls performing high working memory load tasks, the HPC deactivates and functionally uncouples from the dlPFC. Such an anticorrelated pattern is, however, disrupted in chronic and first-episode patients with schizophrenia and individuals at high-risk of psychosis.[249] This observation has been replicated in several studies using different methodologies. The HPC-dlPFC hyperconnectivity present in schizophrenia may be detrimental to executive processes because of the interference of other cognitive processes such as parallel encoding in episodic memory.[250] This is in line with the suggestion[251,252] that encoding processes are central to memory impairments in schizophrenia, as the storage and retrieval procedures are mostly unimpaired.[253-257] The notion of HPC-PFC hyperconnectivity in patients is also supported by dynamic causal modelling in rats after ketamine injection, which suggests an enhanced drive from the dorsal CA1 to the mPFC, probably mediated by the vHPC.[258]

5.4 | Effects of NMDAR antagonists in healthy humans and animals

Ketamine can be safely administered to healthy volunteers and produces schizophrenia-like effects in both humans and animals, providing a valuable translational tool in the investigation of large-scale network discoordination relevant to schizophrenia. Acute administration of ketamine and other NMDAR antagonists corresponds better to acute psychosis or early stages of schizophrenia because it mimics both positive and negative symptoms, while prolonged treatment (used in rodents) models more closely chronic schizophrenia.[120] Moreover, first-episode and chronic patients can display opposite patterns of FC in the same region[259] and from the standpoint of FC, acute ketamine administration also

models early stages of schizophrenia better than later stages of the disorder.

In general, several rs-fMRI studies have consistently showed that acute ketamine administration mostly increases brain haemodynamic activity (BOLD signal) and robustly enhances FC in humans, rhesus monkeys and rats and that the pattern of change in BOLD signal is remarkably similar across mammals (for a recent review see Maltbie[260]). Using graph network analysis, Becker[261] also reported that ketamine induces hyperconnectivity in both humans and rats and, in addition, showed that ketamine causes a shift towards less-integrated and more segregated information processing (decreased global efficiency and small-worldness of the network). Consistently, topological analysis of fMRI data from schizophrenia patients also suggests a less integrated and more diverse profile of FC, ie, hyperconnectivity with less effective connections.[262] The increased FC induced by ketamine could correspond to elevated noise in the system with shallower attractor states as postulated by Rolls[68] and manifest in reduced anticorrelation within the triple network states.[263] BOLD FC measurements are often interpreted in context of the triple network paradigm (or its variations) as in the recent study by Fleming and colleagues,[264] for example. Long-term effects of ketamine, ie, 24 hours and more after its application, are antidepressant (for a review see Ionescu et al[265]) rather than psychotomimetic or dissociative, thus its effects on FC may differ from the acute phase. For that reason, we will briefly discuss only studies that examined fMRI data as measured shortly after or during the ketamine administration. Alterations of brain activation and FC induced by ketamine are related to schizophrenia-like and dissociative symptoms in a regionally specific manner.[266-269]

In healthy human volunteers, studies examining brain activation are consistent in that ketamine reliably[270] and extensively increases BOLD signal in multiple frontal, temporal, parietal and limbic areas as reported by Deakin.[268] Increased activity in the frontal regions, insula, thalamus and striatum was reported by Doyle.[271] Consistently, de Simoni[270] observed increased activity in the thalamus, insula, ACC, PCC and HPC. Similar activation pattern was reported by Höflich.[272] Deactivation was observed in a number of BOLD rs-fMRI studies in the subgenual anterior cingulate cortex (SgACC)[268,270-273] and the medial orbitofrontal cortex.[268,272] Considering functional connectivity (seed-based or global brain connectivity/GBC), generally, an increased pattern of connectivity was observed by most authors (for a review see Maltbie et al[260] and Haaf et al[274]). Shortly, Höflich[272] observed hyperconnectivity between the thalamus and both parietal and temporal cortex; Dandash[267] reported increased FC of the striatum, thalamus, midbrain and PFC; Driesen[266] also observed elevated FC of the thalamus and striatum; and Fleming[264] reported increased FC between the frontal pole, ACC, PCC and insula. Of note, Fleming et al[264] provides

a comparison of the results of their multicentre rs-fMRI ketamine study in healthy volunteers to the rs-fMRI literature concerning at-risk groups, first-episode and chronic schizophrenia patients. Regarding the hippocampus, some authors observed increased FC of the HPC and prefrontal regions.[275,276] Notably, Grimm[275] observed increased FC of the dlPFC bilaterally to only the left HPC, a finding consistent with hypermetabolism of the left CA1 hippocampal region present in clinical high risk individuals that precedes hippocampal atrophy.[196] However, Kraguljac and colleagues[277] reported a decrease in HPC FC with the frontal cluster. Thus, HPC-prefrontal FC seems to be altered by acute ketamine infusion in humans, but the direction of change is unclear and more studies using comparable experimental settings and methods of analysis are needed to elucidate under which conditions ketamine increases or decreases hippocampal FC. In addition, decreased connectivity of the SgACC was observed by Wong.[269]

A number of studies examined the effect of acute ketamine on brain activation and FC in rodents and rhesus monkeys. First, in awake monkeys, ketamine induces extensive activation in the cortical and subcortical regions, including dorsal striatum, thalamus and cingulate gyrus.[278] Also, ketamine increases FC in awake rhesus monkeys between the dlPFC and frontal, striatal and temporal regions (including HPC), and between amygdala, striatum, insula and SgACC.[279] As noted by Maltbie,[260] the regional pattern and magnitude of hyperconnectivity after ketamine observed in rhesus monkeys[278] is similar to that observed in humans[279] wtih the exception of increased FC of the SgACC to cortical and subcortical regions present in rhesus monkeys[278] compared to decreased FC of the SgACC in humans as reported by Wong.[269] Second, in awake rats, ketamine induces extensive activation, including mPFC, striatum, cingulate cortex and HPC.[280] In addition, activity in the periaqueductal grey, VTA, s. nigra and inferior colliculus was decreased.[280] FC assessed in rats under light medetomidine anaesthesia revealed increased connectivity within the PFC, and between HPC, RSC and PFC.[281] A study by Grimm and colleagues[275] examined FC after ketamine administration in both humans (as described above) and rats. While in human subjects the FC of bilateral dlPFC was increased to only the left hippocampus, in rats the FC of PFC (the prelimbic area) was increased to both left and right hippocampus, possibly because of reduced laterality in both molecular profile and structural connectivity.[275]

Next, we briefly note the effects of acute NMDAR antagonists as measured by electrophysiological methods. Importantly, oscillations in the gamma band (a frequency extensively studied in general and also in relation to schizophrenia in particular) and BOLD connectivity in humans are strongly correlated.[282] Electrophysiological methods in rodents have enabled detailed explorations of NMDAR-antagonist-induced network alterations. For example, Palenicek

et al[283] found increased EEG power particularly in the gamma band and coherence virtually across most rat cortical regions after systemic ketamine injection, which may further support the notion of the brain's inability to maintain distinct cortical functional states after the induction of schizophrenia-like symptoms. Similarly, the application of a single MK-801 dose to both HPC and PFC slices from rats causes a marked increase in LFP power in the gamma band.[284] Interestingly, local application to either the PFC or the HPC results in similar changes in oscillatory activity as systemic injection.[285] Similar alterations have been demonstrated in healthy human subjects receiving ketamine. A recent study reported ketamine-induced current source density (CSD) reductions in slow (delta/theta and alpha) and increases in fast (gamma) frequencies, with simultaneous frequency-specific CSD changes in the DMN, CEN and SN.[267] In addition, ratings of depersonalization in individual subjects were associated with alpha CSD reductions in specific regions of interest in each of the 3 networks. Results of this study support the role of hypofunctional NMDA receptor activity in aberrant oscillations of large-scale brain networks in schizophrenia that may contribute to the emergence of perceptual and dissociative symptoms.

6 | BEHAVIOURAL AND COGNITIVE DISORGANIZATION

On the behavioural level, the above-described discoordination of cell populations and large-scale brain networks could produce complex behavioural changes including inappropriate perceptual associations and beliefs, deficits in the integration of contextual information as well as impaired sub-grouping and/or discrimination between relevant and irrelevant information.[286] Moreover, the general cognitive deficits observed in schizophrenia could be attributed to impairments in the binding and coordination of individual cognitive processes and cognitive control. It has also been proposed that cognitive deficits observed in a broad range of domains may be understood in terms of impaired contextual processing of task-relevant information.[287-289] This hypothesis has been supported by numerous experimental studies (for a review see[290]). HPC ensembles are essential for the encoding of contextual information and prevention of interference.[16]

6.1 | Coordination of contextual information

The binding and discrimination processes that depend on contextual information are essential for episodic memory formation.[291] Contextual binding allows us to combine different contextual elements into a complete memory representation and provide us the knowledge that certain features—content and context, spatial relationships and/or temporal order—have co-occurred.[292] Indeed, human studies applying memory binding tasks, such as the remembering of both a target (words, objects or faces) and its spatial position or other context feature such as temporal order[252,293,294] indicate that the memory for target or spatial information alone is unimpaired in schizophrenia, but the ability to bind target and spatial information is compromised. Medial temporal lobe structures, particularly the HPC, play a critical role in this type of contextual binding in humans.[16,295]

Evidence for such discoordination of contextual information has also been reported in animal models. Psychotomimetic manipulations both pharmacological (MK-801, ketamine or PCP) or developmental (NVHL) affect cognition, especially in situations where the coordination of different, competing representations or memories is required.[58,61,177] This can be demonstrated in a place avoidance task using a slowly rotating arena, a circular apparatus with transparent walls, sometimes referred to as Carousel; for a review, see Stuchlik et al.[296] Variants of a place avoidance task in a Carousel are illustrated in Figure 6. The Carousel task can be used to study cognitive control and the coordination of contextual information at both behavioural and neurophysiological levels.[297] In the most widely used standard Room+Arena- variant (also termed active (allothetic) place avoidance or AAPA), with frames of reference dissociated, the animal is reinforced by a mild foot shock to avoid a shock zone spanning 60-deg of the arena surface defined in the coordinate frame of the room. Successful performance in this variant depends on using relevant spatial information (ie, room landmarks) and ignoring irrelevant information provided by cues on the rotating arena itself (self-generated scent marks). The Room+Arena- version is analogous to the Stroop test used in human subjects (see below) in the regard that only one stream of information (the colour/room-frame) is to be used while the other (meaning of the written word/arena-frame) has to be ignored. Performance in this variant of the Carousel is particularly affected in animal models of schizophrenia.[58,61,177] Importantly, the performance of schizophrenia models is unaffected if the conflict between the arena- and room-frame is removed by submerging the arena in shallow water, thus suppressing the arena-bound cues (Room+condition). This observation supports the conclusion that it is the coordination of contextual information, and not motivation or spatial navigation, that is affected in schizophrenia models.[61]

Successful performance in the Carousel task requires coordinated grouping of HPC neurons into ensembles that represent dissociated frames of reference and switch dynamically according to changing behavioural needs.[52] Neurobehavioral deficits in cognitive control and contextual binding are accompanied by deficits in neural coordination on the cellular level as well as on the level of LFP. Unilateral inactivation
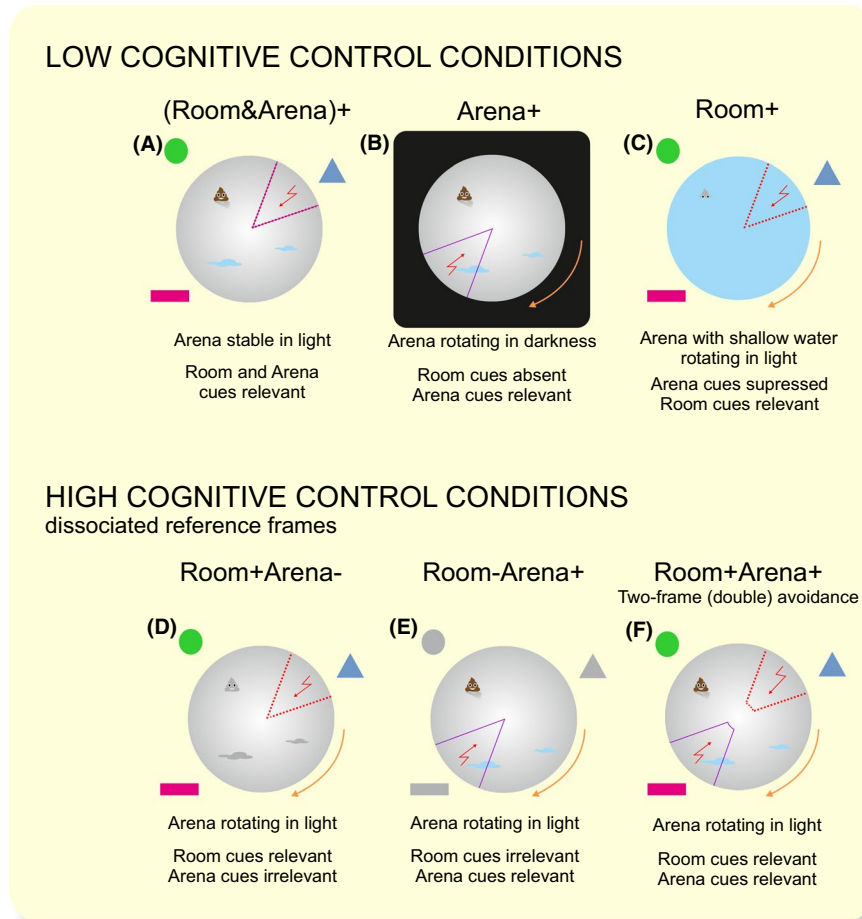
FIGURE 6 Variants of the place avoidance task conducted in a carousel. Symbols outside the arena represent extra-maze cues, self-generated scent marks serve as arena cues. Grey-coloured cues are present but not relevant. Conditions A, B, C place low demands on cognitive control processes since cues in different reference frames are not in conflict. Conditions D, E, F require high levels of cognitive control because of dissociation of cues in different reference frames. A, (Room&Arena)+ avoidance. Arena is not rotating, cues from both frames of reference are available and relevant and there is no conflict between reference frames. Foraging is necessary to prevent passivity. B, Arena+ avoidance. Arena is rotating in darkness, no room cues are available and a shock is defined in the arena-frame; therefore, no information conflict is present. Foraging is again needed to prevent passivity. C, Room+ avoidance. Arena is rotating in light but its surface is covered in shallow water (~1 cm), thus substratal cues are hidden and conflict between the dissociated room and arena reference frames is attenuated. D, Room+Arena– avoidance (active allothetic place avoidance [AAPA]). Arena is rotating in light, cues from both frames are available but only room cues predict the shock. Animals must ignore arena-bound cues and actively avoid being brought to the shock sector. Foraging is not required, but improves avoidance performance. E, Room–Arena+ avoidance. Similar to condition D but the shock sector is defined in the arena-frame. Foraging eliminates solving the task by not moving. F, Room+Arena+, 2-frame (double) avoidance. Two shock sectors are present, one defined in each frame. Both sectors are truncated from the centre of the arena to provide an opportunity for escape when rotation brings the 2 sectors together. Arena is rotating in light, both frames of reference are present and both are relevant. This is the most difficult version of the task. Image adapted from Stuchlik et al[296]

of the dorsal HPC by TTX, which causes an impairment in cognitive control measured as impaired place avoidance in the Room+Arena- task,[297] also causes impairment in the coordination of neuronal discharge between HPC neurons.[59] This neural discoordination takes the form of a hyper-synchrony of firing between originally negatively correlated cell pairs, and an altered coordination of ensemble firing.[58,59] On the level of LFP, cognitive control deficits are related to increases in medium/fast gamma (60-100 Hz) power in the HPC[58] and to desynchronization of LFP across hemispheres in a broad band of frequencies including the beta and theta range.[177,178] The relationship between cognitive deficits and neuronal discoordination is supported by the observation in rats that pharmacological and behavioural manipulation (adolescent cognitive training) that attenuate cognitive control deficits also attenuate neural desynchronization.[177,178]

Cognitive control impairment has also been tested in patients with schizophrenia using a Carousel task adopted for humans—the virtual Active Allocentric Place Preference task (vAAPP).[298] First episode schizophrenia (FES) patients showed generally lower performance in comparison to matched healthy volunteers in all task variants. However,

while the Arena+Room- condition showed learning-related improvements in FES the performance in Room+Arena- task showed much stronger and stable impairment. In the context of the dissociated reference frames (subsets of cues) that have to be correctly discriminated in order to correctly solve this hidden goal task, these results support the hypotheses of the general impairment in cognitive control reported in animal studies.[61,299,300]

Similarly, the Stroop task, which is the most commonly applied measure of focused attention and cognitive control in humans, requires the subject to distinguish between relevant and irrelevant information. The conflict between the verbal information and visual information (in naming the printed colour of a word when the word is itself the name of another colour) creates interference that must be suppressed in order for the tested individual to perform well. Stroop task performance was previously associated with frontal lobe functions; however, in terms of pattern separation and conflict of information provided, HPC activation has also been reported.[152] Patients with schizophrenia indeed exhibit an increased interference effect (increased reaction time and number of errors) repeatedly demonstrated in the traditional Stroop task (for review see[301]). Interestingly, in Stroop variants with colour-congruent information, patients with schizophrenia show augmented facilitation, ie, faster responses to congruent than to neutral trials.[302] This observation can be accounted for by an increased precision of priors in Bayesian terms. Overall, these findings suggest that patients fail the task only if multiple (distracting) attentional demands appear[301] that require discrimination between the irrelevant verbal and relevant visual information provided, thus supporting the above-mentioned model. This observation is in line with the preserved performance of animal models in the "low-conflict" variants of the Carousel task as reported above.

6.2 | Cognitive flexibility

Schizophrenia patients and animal models of the disorder display inflexible cognition and behaviour. Cognitive flexibility, the ability to adaptively change one's behaviour in response to new environmental requirements or altered contingencies emerges from cognitive functions such as attention, salience detection, working memory, response inhibition and switching.[15] Cognitive flexibility consists of task switching and (attentional) set-shifting.[15,303] The latter may be intra- or extra-dimensional[304] and requires adoption of a new set of rules to successfully accomplish the same task.[15]

Impaired cognitive flexibility has been demonstrated in patients with schizophrenia in various task/set-switching paradigms related to hypofunction of the PFC.[305,306] A typical example of a set-shifting task used in human studies is the Wisconsin Card Sorting Test (WCST)[307,308] that requires the subject to discover and follow simple but specific rules when

sorting cards into predefined categories (sets). As the rules applied in the task change randomly over the trails, the task demands switching between these rules and therefore performance represents a measure of cognitive flexibility. Deficits in such set-shifting abilities, as measured by the Wisconsin card sorting test,[309-311] are well-documented in patients with schizophrenia. Patients successfully sort fewer categories than healthy subjects, show difficulties in maintaining a set and show a high rate of perseverative errors, which may reflect rigidity—an inability to abandon a response that was previously correct after receiving negative feedback. Deficient extra-dimensional set-shifting in patients is also documented by the intra-dimensional/extra-dimensional (IDED) set-shifting task that is homologous to those used in rodents.[304] In addition, patients also display deficits when irrelevant stimulus (distractor) is introduced during the IDED task.[312]

Deficits in set-shifting are also present in schizophrenia animal models.[304] For example, systemic administration of MK-801 impairs set-shifting abilities in rats in the Carousel task, while cognitively less demanding reversal learning on Carousel remains unaffected.[313] A study by Cho and colleagues[314] points to the crucial role of GABAergic interneurons and PFC in cognitive flexibility. Specifically, inhibition of PFC interneurons in control mice disrupts cognitive flexibility tested in an attentional set-shifting task and stimulation of PVIs at 40-60 Hz (gamma-band) in mice heterozygous for $Dlx5/6$ ($Dlx5/6^{+/-}$) normalizes their otherwise impaired cognitive-behavioural performance.[314] $Dlx5/6$ is a transcription factor that regulates the development of PVIs.[315] $Dlx5/6^{+/-}$ mice display abnormalities in PVIs, gamma rhythms and cognition that emerge only after adolescence, similarly as in patients with schizophrenia.[314] Thus, disrupted E/I balance and neural discoordination are plausible mechanisms of cognitive inflexibility. However, more detailed studies examining the ensemble code as related to flexible behaviour are needed.

7 | DISCUSSION AND FUTURE OUTLOOKS

7.1 | The concept of schizophrenia and its utility for neuroscientific research

The validity and usefulness of the concept of schizophrenia as a guide for research and new treatments[316] has been repeatedly questioned on the grounds that its definition is based on phenomenology, which likely does not map onto neurobiology.[317-320]

Despite the diagnostic utility, the phenomenologically defined symptom categories indeed might not act as optimal guides for neuroscientific research. First, the 3 symptom categories—positive, negative and cognitive—may not

have distinct and corresponding counterparts in neurophysiology. Second, the disorganization aspect of schizophrenia might constitute a dimension separate from positive symptoms.[321] Third, the boundaries between symptom categories might not hold, as hallucinations, delusions, disorganization and some aspects of negative symptoms may in fact be secondary and stem from underlying cognitive dysfunctions.[160,166,172,187,322-324] Fourth, many abnormalities are well documented in patients and their first-degree relatives, but they are not included in the diagnosis of schizophrenia. These could be more proximal manifestations of underlying neuropathology and therefore valuable for neurobiological inquiry into the basis of schizophrenia. Examples include alterations in perceptual and neurocognitive tasks, resistance to optical illusions and neurological soft signs.[289,325-330]

The problem of category definitions and mapping onto neurophysiology also holds true for the nosological unit of schizophrenia itself. The signs and symptoms may vary dramatically between patients. Moreover, the clinical overlap between schizophrenia, schizoaffective and bipolar disorder is substantial, and the evidence for distinct phenotypes clustering around traditional phenomenological units is scant.[331] This lack of specificity of neurobiological findings in schizophrenia may render the search for a single common pathway an unattainable goal.[317] Distinct pathophysiological trajectories and compensational mechanisms might give rise to similar signs and symptoms and result in a single diagnostic label. For example, antibodies targeting GABARs,[332] NMDARs[333] or potassium ion channels[333] can all lead to schizophrenia,[334] as is also true for microdeletion in the 22q11.2 chromosomal band.[335]

A dimensional approach that cuts across traditional nosological units and focuses on intermediate phenotypes and endophenotypes seems more appropriate for research purposes. The Research Domain Criteria (RDoC) developed in recent years by the NIMH, USA, exemplify such an attempt.[318,336] In addition, psychosis symptoms may exist on a continuum, in which one of its dimensions may span from the false sensory experiences and misattribution of agency that occur quite commonly in the general population, through alogia and the peculiar beliefs of schizotypy, to the extremes of hallucinations, delusions and detachment from reality as observed in acute psychosis. Similar continua may exist with regard to neurocognitive and affective aspects.[320,337]

7.2 | Disinhibition and the discoordination hypothesis

Neural disinhibition, ie, increased activity of principal cells as a result of diminished inhibitory control by interneurons, is a widely applied framework that attempts to explain cognitive impairments and psychosis-like symptoms associated with psychotomimetic drugs. However, the discoordination hypothesis posits that disorganized patterns of neuronal activity, even in the absence of an increase in the overall firing rate, are responsible for cognitive deficits and psychotic symptoms.

A number of studies have investigated the effects of psychotomimetics on neuronal activity in vivo.[57,58,129,338-341] Other authors have explored neuronal disinhibition as related to schizophrenia in a more general approach using GABAR agonists.[127,342,343] These studies differ in experimental procedures such as the drug applied, dosage, type of administration, site of electrical recording, parameters studied and the status of the animal, thus providing heterogeneous results. For example, in a highly influential study Homayoun and Moghaddam observed neuronal disinhibition, ie, an increase in firing rate of principal cells that is preceded by a decrease in the activity of putative interneurons, in mPFC neurons in vivo after MK-801 administration.[129] Similar observations of an increase in firing rate in the mPFC were reported by Molina et al[340] and by Jodo et al[339] in the ventral HPC (vHPC) after PCP treatment. On the contrary, no increase in overall firing rate was observed in dorsal HPC (dHPC) pyramidal cells after PCP in awake animals[58] or after MK-801 in anaesthetised rats.[57] However, more research that compares how neuronal coding is disrupted in psychotomimetic and other schizophrenia models in different parts of the brain, such as the mPFC and HPC, is needed.

The notion that psychotomimetic effects are related to the disorganization of neuronal activity rather than to disinhibition in terms of increased firing rate is supported by the following observations. Wood and colleagues[341] applied 3 different types of psychotomimetics—MK-801, amphetamine and DOI (1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane)—related to 3 different neurotransmitter systems, namely the glutamatergic, dopaminergic and serotonergic respectively. Of these psychotomimetics, only MK-801 increased neuronal activity in the PFC, while DOI-dose dependently decreased the firing of principal cells and amphetamine had no substantial effect on neuronal spiking. Notably, the disorganization of neuronal discharge has been reported in several studies after the administration of NMDAR psychotomimetics regardless of the presence of increased firing rate.[58,338,340,341] In complement to studies that induced disinhibition more or less directly,[127,342,343] inducing local disorganization of neuronal discharge without increasing firing rate would be an intriguing albeit technically demanding approach to explore the causal roles of disinhibition and discoordination in schizophrenia models.

7.3 | Memory allocation and ensemble discoordination

When learning occurs, the memory trace has to be allocated to some subset of neurons. This ensemble acts as a

representation of a given memory on the neurobiological level and enables memory storage and recollection. To support adaptive cognition and behaviour, memories are linked so that recollection of one invokes another, related memory. The neurobiological processes of memory allocation and linking has been, to some degree, elucidated in recent years by a number of ingenious experimental studies that directly manipulated the memory trace (reviewed in[44,344]). Briefly, memory is allocated to neurons with increased excitability, a process mediated by CREB. Also, learning itself increases intrinsic excitability in recruited neurons.[345] Because memory is allocated to more excitable neurons and learning increases excitability, it follows that allocation of the first memory biases allocation of a second memory to largely the same neurons, thus increasing ensemble overlap and linking the 2 memories together.[346] Altered excitability would affect memory coallocation and linking. Decreased neuronal excitability, as present in aged mice, impairs coallocation of 2 distinct memories and impairs memory linking on the behavioural level.[347] On the contrary, excessive memory linking was observed after the enhancement of excitability in lateral amygdala neurons induced by chronic stress.[348] Our observations of increased overlap of ensembles representing 2 distinct contextual experiences after a psychotomimetic dose of MK-801[61] suggests the hyperexcitability of HPC neurons and excessive memory linking, consistent with hyperassociations observed in patients with schizophrenia. Further studies of excitability, memory coallocation and linking utilizing various schizophrenia models such as NVHL or maternal separation would be informative since they do not interact directly with NMDARs at the time of measurement—that is, with receptors involved (via Ca2+ influx) in probing ensemble overlap either by calcium imaging or fluorescence in situ immediate-early gene imaging.

7.4 | Dynamic switching in large-scale networks

With respect to altered cognitive control and coordination as the core of the general cognitive deficits observed in schizophrenia, we suggest that cognitive assessments in schizophrenia should apply more complex and ecologically valid spatial cognitive tasks that would allow us to address functional HPC-PFC connectivity in the context of large-scale networks. The frontotemporal connectivity could be specifically studied using virtual tasks that would require navigation in complex environments (such as city environments) or in tasks aimed at the recollection of recently acquired episodic memories in order to provide a requested behavioural response. Events of spatial or memory-related decisions that first require the recollection of some information and subsequent decision-making with an active behavioural response could be used to identify events of coordination and fast switching between brain networks related to specific internally or externally oriented cognitive processes.

8 | GENERAL CONCLUSION

Past and recent evidence suggests that disruptions of neuronal and neural coordination observable at different levels of resolution could be viewed as substrates of cognitive control and other high-order functional deficits in schizophrenia. Cognitive deficits form relatively stable and partly heritable phenotypes of the disorder, and are present both in patients with schizophrenia and in multiple animal models of various origins. Further research will elucidate if these manifestations relate to the pathophysiology of schizophrenia, but the data currently available suggest that they form a core component of this disorder, which could also explain other seemingly distant deficits such as aberrant percepts (hallucinations) and thoughts (delusions). The details of insight are relatively coarse in human patients, being limited by the resolution of neuroimaging methods, stressing the utmost need for valid animal models in which novel techniques of ensemble mapping and manipulation may be implemented. Transition to dimensional approach to neuropsychiatric disorders with focus on intermediate phenotypes will enable detailed examination of underlying mechanisms unconstrained by phenomenologically defined psychiatric diagnostics that blends patients of heterogeneous pathophysiology into a single nosological group named "schizophrenia."

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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