The Shallow Cognitive Map Hypothesis: A Hippocampal framework for Thought Disorder in Schizophrenia

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Abstract

Memories are not formed in isolation. They are associated and organized into relational knowledge structures that allow coherent thought. Failure to express such coherent thought is a key hallmark of Schizophrenia. Here we explore the hypothesis that thought disorder arises from disorganized Hippocampal cognitive maps. In doing so, we combine insights from two key lines of investigation, one concerning the neural signatures of cognitive mapping, and another that seeks to understand lower-level cellular mechanisms of cognition within a dynamical systems framework. Specifically, we propose that multiple distinct pathological pathways converge on the shallowing of Hippocampal attractors, giving rise to disorganized Hippocampal cognitive maps and driving thought disorder. We discuss the available evidence at the computational, behavioural, network and cellular levels. We also outline testable predictions from this framework including how it could unify major chemical and psychological theories of schizophrenia and how it can provide a rationale for understanding the aetiology and treatment of the disease.

Introduction

The ability to translate our experiences into coherent thoughts is central to our daily function. A stark reminder of this comes from appreciating thought disorder, one of the key hallmarks of schizophrenia. Patients exhibit incoherent, undirected speech, often making inappropriate associations between unrelated experiences and concepts^{1,2}. This can have a debilitating effect on their ability to communicate and function in society. A key challenge in schizophrenia research has been to understand the ontogeny of such disorganization, in the hope of developing more effective treatments. To achieve this, it is necessary to first understand how our experiences are associated to form organized models of the world, which in turn gives rise to organized thought.

One of the key breakthroughs in psychology has been the conceptualization of the cognitive map. This theory posits that animals not only form associations between directly experienced events, but also organize such relationships into coherent structures that enable flexible inference³. Animals can find shortcuts in mazes along paths they have never traversed, after mapping the relationship between the different locations they have visited. Analogous inferences can be made in the non-spatial domain, where distinct experiences can be associated to infer new links that together build a coherent model of the world⁴⁻⁶. Knowing that $A > B$ and $B > C$ allows inferring that $A > C$, but only if memories of the A-B and B-C associations are *organized* on a line. In the search for a neural basis of such cognitive mapping, research on the Hippocampus and associated regions in the medial temporal lobe has been particularly fruitful. Lesion, inactivation, neuroimaging and electrophysiological studies across multiple mammalian species implicate

such circuits in forming relational maps of the world and enabling inferences^{7,8}. That Hippocampal pathology is also strongly implicated in schizophrenia raises the possibility that thought disorder may be the result of disorganized Hippocampal cognitive maps. Here we review the latest evidence suggesting a convergence of multiple distinct mechanisms and aetiological pathways on disorganized Hippocampal maps. We begin by outlining and motivating the ***shallow cognitive map*** hypothesis. We then explore three key predictions of this framework and outline evidence from schizophrenia patients and animal models speaking to each prediction. We note that schizophrenia is not a solely Hippocampal disorder, and pathologies in areas such as the Prefrontal cortex have been strongly implicated in the disease^{9,10}. Our focus here is on the Hippocampus, since it is there that we understand the most about mechanisms behind cognitive mapping. Nevertheless, insights from exploring shallow cognitive maps in the Hippocampus may well generalize to other cortical drivers of the disease.

The shallow cognitive map hypothesis of Thought disorder

How does thought disorder arise in schizophrenia? One prominent idea frames this question within the dynamical systems framework, especially implicating the concept of attractors. Attractors are stable states of activity towards which a complex system (e.g. a neural network) evolves. Several stable states, representing distinct memories, may exist within the same network. A particular sensory cue biases the network to evolve towards a particular attractor state, one that was perhaps associated with the cue during learning. Owing to its stability, the network persists within an attractor state beyond the initial stimulus, thereby facilitating faithful memory retrieval¹¹. Such attractors can be discrete, reflecting the activity of a defined assembly of neurons¹¹. They can also be continuous, wherein the network moves between a constrained set of states (or assemblies) with minimal perturbation¹². Attractor dynamics can be implemented by recurrent excitatory (glutamatergic) synaptic connectivity, which promotes positive feedback and hence persistent activity amongst assemblies of strongly connected principal neurons. GABAergic interneurons control such activity, in part by inhibiting the spread of activity *between* assemblies. This is essential in defining the attractor “valley” (**Figure 1A left**), reducing the prevalence of “jumps” between distinct attractors. Learning can stabilize existing states or generate new stable states through promoting synaptic (and cellular) plasticity in the network. The greater the *relative* depth (stability) of the attractor state, the longer a network can persist there and hence the lower the likelihood of jumping between states due to distractors or intrinsic noise. This is proposed to ensure the retrieval of memories, and hence the flow of thoughts, is both coherent and goal appropriate. It is hypothesised that shallow cortical attractors could give rise to thought disorder by reducing the threshold for switching between attractor states^{13–15}. We extend this idea with a specific emphasis on Hippocampal attractors involved in cognitive mapping.

Hippocampal cognitive mapping is particularly implicated in forming internal models that map the links between memories, even when all the links have not been directly experienced^{6,7}. Such “relational” mapping of disparate elements of experience is central to internal cognitive capacities such as imagery, inference and thought¹⁶. However, dysregulated, excessive or inappropriate associations may give rise to disorganized and debilitating thought. We propose that the shallowing of attractors in the Hippocampus may have the specific effect of disrupting the formation and/or retrieval of Hippocampus-dependent cognitive maps, and hence give rise to the aberrant associations expressed in thought disorder (**Figure 1a**). During memory formation, this lowered threshold for jumping between attractors could alter the integrity of the memory stored, by permitting aberrant Hebbian associations between unrelated memories. During memory retrieval, the reduced stability of attractors for any particular memory means the threshold for switching between attractors, and hence memories, is lowered (**Figure 1a**). In both cases, the end result would be the generation of disorganized maps that inappropriately relate separate events or memories, with this disrupted relational mapping resulting in thought disorder. We therefore propose that:

Thought disorder in schizophrenia is mediated by disorganized cognitive maps resulting from the shallowing of neural attractors in the Hippocampus.

By considering the phenomenology and mechanisms underlying cognitive mapping in light of this hypothesis, a number of predictions arise. Below we outline these predictions, critically assess existing evidence pertaining to each and, where appropriate, suggest future experiments that address the current gaps.

Prediction 1 - Thought disorder is caused by disorganized Hippocampal relational representations.

A key hallmark of cognitive mapping in the Hippocampus is the phenomena of replay. This classically refers to the sequential reactivation of spatial representations during offline rest/sleep reflects the spatial structure of the environment, with adjacent locations being reactivated contiguously in the absence of the relevant sensory input¹⁷. In the Hippocampus, this replay typically occurs during brief periods of high neural synchrony characterized by sharp-wave ripples (SWRs; irregular deflections (sharp waves) associated with 140-200Hz oscillations (ripples)) in the local field potential generated during slow-wave sleep or periods of awake immobility¹⁸. That this replay occurs in the absence of structured experience suggests an *internal* organization of representations, reminiscent of Tolman’s postulated cognitive maps. Moreover, such SWR-associated replay has been implicated in memory retrieval in humans^{19,20} and rodents²¹ (but see Gillespie et al 2021²²). Similarly, theta oscillations occurring during online locomotion in rodents are associated with the ordered firing of place cells that represent the spatial organization of

visited locations, albeit in a temporally compressed manner²³. Such “theta sequences” are implicated in the encoding and retrieval of memories²³. The sequential reactivation of representations in both replay and theta sequences can be (re)framed in terms of attractor dynamics²⁴. A replay event can be understood as a trajectory through an attractor valley that respects the relational structure of a particular state space. States of the world that are more closely related are closer on the neural activity space, and hence reactivated more closely together, than more distantly related states. Crucially, such replay is not merely a recapitulation of experienced associations. States that have not been explicitly experienced together, but whose close relationship can be inferred by understanding the relational structure of the state space, are contiguously replayed^{25,26}. This phenomenon is proposed to underlie the process of **relational** inference itself, allowing coherent thoughts and insights to emerge from explicit memories in the healthy mind²⁷. This could be achieved by selectively lowering the threshold for jumping between attractor states representing distinct but related memories, effectively shallowing the attractor landscape only for transitions between these memories. If this process is dysregulated it would manifest as disorganized replay, where parts of sequences representing unrelated memories are excessively and inappropriately intermixed (**Figure 1b**). This may be especially associated with the positive (psychotic) state and particularly with thought disorder episodes.

Emerging evidence from patients and animal models suggests that offline replay is impaired in schizophrenia. In a recent study, Nour et al used Magnetoencephalography (MEG) to investigate offline replay of task representations in schizophrenia patients learning a structural inference task²⁸. The authors used a task that involved learning a sequence of visual cues from separately experienced 1-step transitions (e.g. A->B; B->C...etc). While patients were unimpaired in remembering such 1-step transitions, they were impaired in using such experiences to transitively infer ordinal relationships that had not been explicitly observed (e.g. A->C²⁸). This could not be explained by more basic deficits in working memory or rule comprehension. Such an impairment is consistent with earlier results showing selective impairments in relational processing but not retrieval of directly experienced associations in schizophrenia²⁹. Crucially, Nour et al show that such a behavioural impairment was associated with impaired spontaneous (off-task) replay of sequential relationships between items. In both patients and controls, this replay was coincident with increased Hippocampal ripple power. However, schizophrenia patients exhibited an augmented ripple power relative to controls. This combination of impaired replay and enhanced Hippocampal ripple power mirrors that previously observed in mouse models of schizophrenia^{30–32}; and is consistent with a strong involvement of Hippocampal offline replay in the expression of schizophrenia symptoms.

A number of key questions remain. First, whether *Hippocampal* replay is selectively impaired in human patients is unclear from the MEG analysis. Concordance with Hippocampal ripples suggests a Hippocampal involvement. This may reflect impaired replay in the Hippocampus, as seen in mouse models^{30,31}. Alternatively, the observed human deficits could reflect impaired cortical replay, which can co-occur with Hippocampal ripples³³. Second, while results from humans and animal models show *impaired* replay associated with schizophrenia, they fall short of showing *disorganized* replay. Replay impairment may simply reflect a loss of function, in which relational associations are weak or absent. Alternatively, it may represent a disorganization, where aberrant relational associations are made resulting in parts of distinct sequences being erroneously stitched together, as we propose here (**Figure 1b**). Nour et al did not find evidence for any specific instance of such disorganized replay. Such an absence of evidence may reflect methodological constraints of testing for the presence of a particular pattern of disorganized replay³⁴. In addition, replay was assessed in an off-task rest session. It is possible that replay (or other forms of organized, sequential activity, such as theta sequences) is disorganized during the process of inference itself in schizophrenic patients. Consistent with this, the authors find evidence for disorganized representations *during* task performance in schizophrenia. Using representational similarity analysis in the visually evoked MEG data from a post-learning task, the authors report that controls exhibited representations that were more similar for items in equivalent positions across two sequences. In contrast, schizophrenia patients exhibited representational similarity patterns that systematically confused adjacent items both within and across sequences. Such a deficit is consistent with disorganized cognitive mapping in schizophrenia. Third, it is not clear whether and how the impaired replay and representations are related to thought disorder. Nour et al find that both the strength of abstract position representations and replay are positively correlated with sequence learning in patients and controls. This may hint at a relationship to ordered thought. However, the authors did not find a relationship between the severity of positive symptoms, as assessed using the Positive and Negative Symptom Scale (PANSS), and behavioural/neural signatures of sequence learning. This may reflect the typically narrow and low range of symptom severity of patients that can be recruited to such studies. In particular, patients with severe thought disorder are typically excluded from such studies due to ethical considerations. It may also reflect the assessment of replay during off-task periods. On-task replay may be more closely linked to symptoms, especially thought disorder. A related question is the extent to which online theta sequences are impaired in schizophrenia. A plethora of studies point to the reduction in the power of theta and associated gamma (25-100Hz) oscillations in schizophrenia³⁵, rhythms strongly implicated in temporally organizing neural ensembles and cognitive mapping functions³⁶. Moreover, findings from animal models of schizophrenia are consistent with aberrant theta-based organization of neural firing³⁷. Whether and how these relate to psychotic symptoms in patients remains unclear.

The study by Nour et al provides a unique insight into the role of cognitive mapping in schizophrenia. Future experiments will need to clarify whether it is the Hippocampal sequences that are impaired, or whether Hippocampal involvement relates to its permissive role in the generation of cortical sequences, e.g. via SWR-mediated Hippocampal-cortical interactions³⁸. Combining the spatial resolution of functional Magnetic Resonance Imaging (fMRI) with temporal resolution of MEG³⁹ could allow investigating the relative roles of Hippocampal and cortical replay deficits in schizophrenia. Moreover, the relationship between Hippocampal activity and thought disorder is currently unclear. Studies using positron emission tomography and cerebral blood volume measurements with MRI show increased resting-state Hippocampal activity in schizophrenia patients^{40–42}. This hyperactivity is positively correlated with psychotic symptoms⁴² and could predict progression from prodromal to psychotic states⁴¹. Conversely, studies in patients performing Hippocampus dependent tasks suggest reduced Hippocampal activity. In a task where patients were required to navigate towards goals in a virtual town, both contextual binding performance and fMRI-deduced Hippocampal/paraHippocampal activity was significantly decreased compared to controls⁴³. While several factors may explain such a discrepancy (e.g., cross-study differences in medication status and disease classification/stage), an intriguing possibility arises from considering differences in behavioural state. Increases in offline Hippocampal activity and ripple power could reflect a compensatory effect that counteracts an online loss of function. Indeed, Nour et al find that, while Hippocampal ripple power is enhanced in schizophrenia patients, ripple power during post-learning rest is actually positively correlated with subsequently measured neural signatures of sequence learning in patients (but not controls²⁸). This is consistent with enhanced offline ripple activity compensating for the impaired relational processing observed in this task, perhaps by promoting cortical replay. If such an enhancement of activity is compensatory then one would predict it would differ depending on disease state and medication, potentially explaining discrepancies in the literature. These considerations highlight the need to move beyond simple descriptions of monotonic changes in overall Hippocampal activity and towards an understanding of the representational and dynamical aspects of Hippocampal activity in relation to defined symptoms. They also implore the inclusion and careful stratification of symptomatically broad cohorts of patients in future studies, in order to avoid confounds relating to symptom heterogeneity. Overall, the hippocampal replay deficits reported in schizophrenia patients and models implicate aberrant *internal* hippocampal relational mapping in thought disorder. However, a more explicit assessment of the nature (disorganization versus loss of function) and timing (rest versus task engagement) of replay impairments and its relationship to the expression of thought disorder is needed to thoroughly assess our prediction.

Prediction 2 - Hippocampal circuit pathology in schizophrenia converges on the shallowing of Hippocampal cognitive maps.

A range of Hippocampal pathologies have been implicated in schizophrenia. These include reduced Hippocampal inhibition⁴⁴, both decreased^{45,46} and increased⁴⁷ long-term potentiation (LTP) at CA3-CA1 synapses, impaired pattern separation in the dentate gyrus/CA3^{48,49}, enhanced pattern completion in the CA3^{48,50}, CA3-associated aberrant salience⁵¹ and impaired goal representations in the CA1³². Here we highlight how these seemingly disparate circuit level pathologies could all converge on the shallowing of Hippocampal attractors and disorganization of cognitive maps.

Imbalance of Pattern separation and Pattern completion

The integrity of cognitive maps necessitates forming appropriate associations between related memories. This in turn relies on the balance between two processes: pattern separation (PS) and pattern completion (PC). An imbalance in PS and PC towards reduced PS and enhanced PC is hypothesized to underlie disorganized memories in schizophrenia (**Figure 2**)⁴⁸.

In PS, similar but unrelated memories are separated in order to avoid interference. Neurons in the dentate gyrus, a key Hippocampal input region, are implicated in this process along with downstream CA3 neurons^{52,53}. Conversely, PC allows linking memory items in order to retrieve a whole memory from partial cues. An analogous process allows linking distinct but related memories in order to infer novel relationships⁵. Strong recurrent excitatory connections between CA3 neurons are implicated in this process^{54,55}. Significant impairments in pattern separation performance are seen in schizophrenic patients, without a significant basic difference in recognition memory compared to matched controls⁵⁶. However, a later study reported an impairment in familiarisation and visual discrimination⁵⁷ in the same tasks employed by Das et al, suggesting the supposed deficit in pattern separation could be explained by lower-level deficits, rather than a selective deficit in pattern separation. A meta-analysis of effects on recognition memory across multiple studies suggests that chronicity (i.e., duration of illness) and (to a lesser extent) PANSS score are key factors: more chronic or pronounced disease is associated with stronger recognition memory deficits⁵⁸. Indeed, patients in the Das et al. and Martinelli & Shergill scored on average 38.82 and 83.92 on the PANSS respectively. This raises the possibility that early (and pre-clinical) stages of schizophrenia could present with more selective deficits in cognitive mapping while the disease may progress to produce low-level deficits in recognition memory.

In addition to behavioural evidence for PS deficits, impairments in both excitatory and inhibitory dentate gyrus (DG) neurons are observed in schizophrenia. Schizophrenia is associated with decreased DG glutamate release⁴⁹ which is partially due to decreased neurogenesis in this subfield⁵⁹. The loss of interneurons in the DG is also implicated in PS deficits, as inhibition is critical for maintaining the sparseness of DG granule cell firing, a feature that is critical for pattern separation⁶⁰. Reduced glutamatergic transmission from DG neurons to CA3 has also been proposed to enhance PC by triggering metaplasticity mechanisms that could lower the threshold for LTP at inputs onto CA3, including those from synapses made by entorhinal cortical inputs and recurrent CA3-CA3 synapses⁴⁸. This would in turn favour the PC mediated by such recurrent connections⁴⁸. Consistent with this, post-mortem analysis of schizophrenia tissue reveals increased GluN2B-containing NMDA receptors (GluN2B/GluN1) in CA3 tissue, but not in CA1⁵⁰. Given the preferential involvement of such receptors in the induction of long-term potentiation⁶¹, this may point to an enhanced capacity for LTP at CA3-CA3 synapses. However, while these results are consistent with an enhanced PC, they do not provide direct support. The loss of PV interneurons, which is also seen in area CA3⁴⁴ may contribute to enhanced pattern completion, by shifting the excitatory-inhibitory balance of CA3 networks towards excitation, and hence promoting aberrant Hebbian associations during memory formation and/or retrieval (**Figure 2; Supplementary Discussion 1**). This would have the effect of reducing the threshold for jumps between attractors during memory retrieval (**Figure 2**). Studies of both synaptic plasticity at CA3-CA3 synapses, network dynamics of CA3 neurons during retrieval and behavioural expression of pattern completion in patients and animal models are needed to establish whether PC is enhanced in schizophrenia patients.

Pathway to shallow attractors: An imbalance of PC/PS tipped against PS would result in forming inappropriate associations between unrelated memories. The threshold for traversing neural states representing such memories is therefore lowered, giving rise to shallow attractors and disorganized cognitive maps.

Aberrant salience

Inappropriate associations and disorganized cognitive maps in schizophrenia may arise due to aberrant salience: the process in which irrelevant stimuli are attributed significance⁶². Subjects at high risk of psychosis attribute greater relevance to irrelevant cues⁶³. A prominent theory, Wagner's model of stimulus processing, suggests that such increased attention to stimuli results from a decreased decay of stimuli from the primary active state to the secondary active state⁶⁴. Such persistence in a highly active state promotes aberrant associations linking irrelevant stimuli⁶⁵.

Aberrant salience has been reported in a mouse model in which the schizophrenia risk gene (*GriA1*) is selectively ablated⁶⁵. This gene encodes the GluA1 subunit of AMPA receptors, which is implicated in Hippocampal plasticity, especially long-term potentiation⁶⁶. GluA1 knockout animals show deficits in stimulus-specific short-term habituation and increased attention to neutral stimulus i.e., aberrant ascribing importance to a non-significant event⁵¹. Crucially, these mice are more readily able to form associations between stimuli⁶⁷ and long-term memories⁶⁷ compared to wildtype controls. Reintroduction of GluA1 selectively into CA2/CA3 restored abnormal short-term habituation as well as the power of, and coherence between, Hippocampal and prefrontal theta oscillations⁵¹. This implicates CA3 function and plasticity in aberrant salience (**Figure 3; Supplementary Discussion 1**). Indeed, recent evidence suggests such Hippocampal dysfunction is a cause for, rather than effect of, the hyperdopaminergic state in schizophrenia⁶⁸. Another recent study found aberrant salience in mice exhibiting a distinct genetic alteration, knocking out PGC-1a KO mice, a gene implicated in schizophrenia and encoding a transcriptional coactivator⁶⁹. These mice exhibited deficits in short-term habituation and decreased PV interneurons in areas CA3 and CA1. Thus, distinct genetic alterations seem to converge on a hyperactive CA3, which seems critical for both aberrant salience and the hyperdopaminergic state in schizophrenia⁶⁷. The circuit mechanisms by which these Hippocampal (especially CA3) deficits mediate aberrant salience, and its relationship (or lack thereof) to imbalanced PS and PC remains an active area of investigation.

Pathway to shallow attractors: Attributing salience to neutral or irrelevant stimuli promotes excessive associative plasticity and hence promotes excessive associations. Similar to PS/PC imbalance, this would reduce the threshold for moving between attractors for unrelated memories in the neural state space and hence result in disorganized cognitive maps.

Aberrant goal attractors in the CA1

Salient locations associated with reward, cues or safety, are represented by more place cells than non-salient locations in the CA1, suggesting a reorganisation of the map towards goals^{70–72}. Such a phenomena was predicted by early continuous attractor models of Hippocampal function, and proposed to arise from enhanced synaptic plasticity at goal locations¹². Intriguingly, in the *Df(16)A^{+/-}* mouse model of schizophrenia, the overnight stability and reward-related stabilisation of CA1 spatial maps was reduced and there was a marked lack of reorganisation of place cells towards goal locations³²(**Figure2, 3; Supplementary Discussion 1**). This may reflect a general phenomenon of shallow attractors in schizophrenia, whereby reduced CA3-CA1 plasticity results in impaired stabilization of assemblies representing goals and paths towards them (**Supplementary Discussion 1**). Indeed, systemic

pharmacological blockade of NMDA-receptors abolishes goal overrepresentation in CA1 and impairs goal-directed behaviour during memory retrieval⁷¹. Alternatively, shallowing of goal attractors may arise from enhanced plasticity (**Supplementary Discussion 1**), as predicted by the aberrant salience hypothesis of schizophrenia. Inappropriately attaching importance to non-goal locations would result in a net under-representation of experiences of true salience and perhaps an inability to recall those most significant when prompted. If everything is a goal, then nothing is a goal.

Pathway to shallow attractors: Reduced synaptic/network plasticity could reduce stabilization of assemblies representing salient states, and hence reduce the deepening of attractors for these states. On the other hand, an enhanced but non-specific (goal-independent) plasticity may also lead to a *relative* shallowing of attractors, as neural states representing non-salient and/or unrelated items are equally deepened (**Supplementary Discussion 3**). In both cases, the network would fail to converge on the appropriate goal-state during memory retrieval, instead jumping between irrelevant states in a disorganized manner. This framework puts the emphasis on attractor landscape and network dynamics, rather than the direction of the activity or plasticity impairment, in mediating thought disturbance in schizophrenia.

Prediction 3 - Molecular changes give rise to thought disorder as a function of their efficacy in shallowing Hippocampal cognitive maps.

It is well established that schizophrenia in general⁷³, and thought disorder in particular⁷⁴, has a heritable component. In addition, epigenetic factors have been strongly implicated in the aetiology of the disease⁷⁵, providing an entry point into understanding environmental influences on schizophrenia. Despite this, no single gene has been identified to be fully penetrant in generating schizophrenia symptoms: schizophrenia is a complex polygenetic disease. Efforts to understand the unifying principles underlying the involvement of distinct molecules and molecular pathways in the disease are therefore critical if its aetiology is to be understood. Genome-wide association studies (GWASs) and gene expression studies have particularly implicated genes related to synaptic function and plasticity^{76–79}. However, lower level cellular processes (such as LTP or interneuron function) alone are insufficient to explain the development of thought disorder. These are both unspecific to the disease (e.g., LTP deficits at CA3-CA1 synapses also associated with Alzheimer's disease⁸⁰ in the absence of psychotic episodes) and often seemingly contradictory (e.g., both enhanced⁴⁷ and impaired^{45,46} LTP reported at CA3-CA1 synapses in Schizophrenia; see **Supplementary Discussion1**). Our framework instead emphasizes a gene's role in deepening of hippocampal attractors as a key predictor of whether its loss-of-function promotes thought disorder. Recent combinatorial genotyping-functional approaches can begin to speak to this. Data from schizophrenia-related GWAS loci have been

integrated with gene-gene network information under a Bayesian framework to better predict risk genes⁸¹. A large proportion of “high confidence” risk genes identified from this analysis were implicated in synaptic development and plasticity (including GluA1 and GluN2A subunits of AMPA and NMDA glutamatergic receptors respectively). Crucially, these genes were enriched in the Hippocampus and frontal cortices, consistent with defective cognitive mapping as a mechanism of schizophrenia. Our framework predicts that:

Functional grouping of genes based on their roles in deepening attractors involved in cognitive mapping processes (via promoting pattern separation, pattern completion, goal overrepresentation, transitive inference...etc) should allow a more accurate prediction of thought disorder prevalence than functional grouping based on lower level processes (e.g. LTP, interneuron function...etc).

While this casts a wide net on a number of processes and pathways, it remains specific: unlike genes promoting deeper attractors, we predict that loss-of-function in genes promoting *shallowness* of attractors (e.g. genes whose function is to downregulate PVN numbers and function) would be protective rather than promote thought disorder.

In order to functionally annotate risk variants highlighted by GWASs, a powerful experimental paradigm has been to investigate the physiological and behavioural effects of disrupting such genes in mouse models. This line of research has repeatedly implicated deficits in processes related to Hippocampal cognitive mapping (See **Prediction 2** and **Figure 3**). We have discussed one such gene (*Gria1*), encoding the AMPA receptor subunit GluA1, where gene knockout results in aberrant salience in a CA3-dependent manner under “**Prediction 2**” above. Other gene knockouts have also yielded insight into the contribution of distinct Hippocampal computations. For instance, GWAS data identified *Rtn4* as a risk gene associated with schizophrenia. Knockout of its functional protein Nogo-A in mice led to hyperexcitability in CA3 circuits and downregulation of mGlu3 metabotropic glutamate receptors⁸². Such hyperactivity may potentially give rise to the enhancement in pattern completion hypothesized to be one mechanism for thought disorder in schizophrenia (**Figure 2**)⁴⁸. While this possibility was not tested, this study did show a behavioural correlate: knockout mice relied more heavily on global (compared to local) reference frames when performing the Morris Water Maze task. Testing animals’ memory retrieval performance in the presence of partial cues would provide a more explicit test of pattern completion in this mouse model, and potentially open avenues for relating gene variants to behavioural stratification of the disease. Moreover, mutations in the plexin family (*Plxna2* / *Plxna4*) of axon guidance molecule receptors are implicated in schizophrenic patients⁸³. Knockout of PlexinA2 in mice results in impaired DG development, neurogenesis and DG→CA3 synaptic connectivity⁸⁴. This may in turn drive the pattern separation deficits seen in

schizophrenia patients (see **Prediction 2**). The same study showed that mice exhibited deficits in Hippocampus-dependent contextual (but not cued) fear conditioning. Nevertheless, a direct demonstration of a pattern separation deficit remains a future prospect.

In addition to the heritable component of schizophrenia, environmental factors are critical in disease aetiology. Epigenetic alterations may provide a mechanistic explanation for the role of such environmental factors^{85–87}. Life events such as childhood trauma are associated with disrupted transcriptional regulation such as hypomethylation of repetitive DNA sequences⁸⁸ and increases in histone deacetylase expression⁸⁹ in schizophrenic patients. These changes have been associated with the plasticity and development of Hippocampal circuits^{90,91}. Can we link such epigenetic changes to Hippocampal cognitive mapping? One promising line of evidence involves the ubiquitous gene repressor, repressor element-1 silencing transcription factor (REST). REST is involved in the age-related maturation of the NMDA receptor from GluN2B- to GluN2A-containing NMDA receptors through epigenetic remodelling⁹². Reduced REST activity in schizophrenia patients coincides with increased GluN2B-containing NMDA receptors in CA3, along with increased postsynaptic density protein-95 (PSD-95) and augmented dendritic spines on the pyramidal neuron apical dendrites⁹². This demonstrates a potential epigenetic basis for markers of increased LTP in CA3. If validated with functional plasticity and behavioural studies, this would suggest a link between epigenetic changes and increased pattern completion, disorganized cognitive maps and consequently, thought disorder. While such a mechanistic link is currently largely speculative, what is clear is that life events, particularly childhood trauma, are linked to Hippocampal changes in schizophrenia⁹³. By combining this line of work with findings implicating synaptic plasticity genes in schizophrenia, we can investigate the extent to which environment-induced epigenetic changes may converge on deficits in synaptic and cellular plasticity underlying the formation of Hippocampal cognitive maps.

Overall, evidence is beginning to shed light on distinct molecular changes that converge on the shallowing of Hippocampal attractors via multiple pathological pathways. A more definitive picture will emerge from stratification of GWAS/transcriptomic results based on the prevalence of thought disorder and annotation of molecular function using a combination of neural ensemble recordings and explicit cognitive tests of cognitive mapping processes (such as pattern separation, pattern completion and transitive inference) in patients and models.

Implications for treatment

The cognitive mapping framework we explore here provides grounding for a combinatorial approach to treating schizophrenia. Across a multitude of psychiatric disorders, it is becoming clear that a combination

of pharmacological interventions and behavioural/psychological rehabilitation (e.g., via cognitive behavioural therapy) might be a highly effective way of alleviating symptoms or even preventing disease onset in the first place⁹⁴. In the context of schizophrenia, we suggest that framing some symptoms as deficits in cognitive mapping allows a more targeted approach on both the drug-based and behavioural fronts (**Supplementary Discussion 2**). Moreover, understanding that multiple heterogeneous aetiological streams could converge on producing shallow, disorganized cognitive maps (**Figure 3**) could allow more personalized interventions (**Supplementary Discussion 2**).

Conclusions and Future directions

Our framework emphasizes shallow attractors underlying Hippocampal cognitive maps as a core mechanism for thought disorder in schizophrenia. This unifies multiple distinct theories of the disorder and promises to explain the heterogeneous aetiology of the disease. We propose that multiple distinct pathologies converge on shallowing of Hippocampal attractors. We have outlined some key predictions from this framework and summarised evidence that pertains to each (see **Supplementary Discussion 3** for additional detailed experimental predictions arising from our framework).

We have primarily focused on Hippocampal pathology and thought disorder in this review. However, schizophrenia pathology is not restricted to the Hippocampus, nor thought disorder. Multiple related regions are implicated, most notably the Prefrontal cortex (PFC).^{9,10} The tight functional interplay between Hippocampus and PFC in mediating cognitive mapping functions provides an entry point into understanding the contributions of these two structures in the aetiology of schizophrenia. Indeed, theta-mediated interactions between the HPC and the mPFC have been implicated in cognitive mapping⁹⁵ and reduced in schizophrenia⁹⁶. Moreover, the PFC has been ascribed its own cognitive mapping functions, most likely providing higher order maps of “task-space”^{97,98} and exhibiting temporally organized “replay” analogous to that seen in the Hippocampus³³. These prefrontal maps are proposed to interact in rich and as yet poorly understood ways with Hippocampal relational maps to mediate flexible, model-based behaviour⁹⁵. Analogous shallowing of attractors underlying prefrontal maps may contribute to thought disorder and/or other symptoms (e.g. delusions and hallucinations). Investigating this possibility at the cellular and circuit levels promises to provide biological grounding to computational models that attempt to unify positive symptoms within a Predictive (Bayesian) framework^{99,100}. We therefore anticipate that the focus on Hippocampal cognitive mapping deficits in schizophrenia will yield broad and generalizable insights into the aetiology of the disease.

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Author Contributions

AM, SK, MM and ME conducted the literature search. AM designed figures 1 and 2 and conducted the associated literature search; SK designed figure 3 and conducted the associated literature search. ME conceptualized the review, wrote the manuscript and revised the figures. AM, SK and MM assisted in writing the manuscript and conceptualizing the review. All authors gave final approval of the completed version.

Competing Interests statement

The Authors declare no competing interests.

Figures

Figure 1: Shallow attractors and disorganized cognitive maps in Schizophrenia

a) Neural state space representing the stability of distinct ensemble activity patterns (two state dimensions, X and Y, are shown for simplicity). In controls, attractors (valleys) representing distinct contexts are stable and well-separated by relatively low stability states (hills). This stability is hypothesized to be reduced in schizophrenia, whereby attractors for distinct contexts are proposed to be relatively shallower. b) A hypothetical instantiation of shallow attractors in Hippocampal cognitive mapping. In controls, place cell activity during learning is replayed during Sharp Wave Ripples (SWR) that occur at rest. Place cell activity from different contexts is maintained separately during replay. This reflects deep attractors, requiring greater jumps in energy barriers to move between attractors of distinct memories. In schizophrenia, place cell activity during learning is replayed during SWRs, however replay is disordered. This may arise due to shallow attractors, in which energy barriers are smaller and easier to cross, making it easier to switch between memories of unrelated contexts during retrieval and hence giving rise to disordered thought.

Figure 2: Hippocampal circuit elements and computations implicated in Schizophrenia

Hippocampal subfields and classical tri-synaptic connectivity (middle right). Impairments at each subfield could contribute to disorganized cognitive mapping. Pattern separation in the dentate gyrus (bottom right panel): Experience of 2 different contexts results in activation of distinct but overlapping neuron groups in the entorhinal cortex (left). Sparse firing of dentate gyrus neurons (top right) reduces overlap in the representation of context A and B, allowing pattern separation in the dentate gyrus. In schizophrenia, pattern separation in the dentate gyrus is reduced (bottom right), reflected by increased overlap in representations of each context. Excessive pattern completion (left panel) may arise through an encoding problem. Here, excessive connections are formed during the initial encoding of the memory, resulting in neurons encoding different contexts having strong connections, which may arise through enhanced LTP (1: top). When partial cues from one context are presented (2: top) the activation of neurons encoding context 1, would also result in the activation of neurons encoding context 2. This could give rise to aberrant Hebbian associations and thought disorder. In controls, only context-selective neurons are activated. Alternatively, a retrieval problem would mean that, when partial cues activate a neuron from a single context (1: bottom), a loss of reciprocal inhibition due to interneuron loss, would result in simultaneous activation of neurons from another context (2: bottom) in patients. Place cells in area CA1 (top right) overrepresent goal locations. This overrepresentation is lost when NMDA receptors are blocked (pharmacological application of CPP) and in genetic models of schizophrenia. This could be seen as a loss of attractors towards goal locations, resulting in disorganized goal-directed behaviour and thought. (panel adapted with permission from Dupret et al 2010⁷¹; color-scale indicates proportion of cells with place field centred at a given location).

Figure 3: Convergence of distinct Hippocampal pathways on Thought disorder

Multiple pathways can give rise to thought disorder, either separately or in concert. Both genetic and epigenetic factors contribute to molecular deficits in key Hippocampal circuit elements. This in turn gives rise to deficits in the activity and plasticity of the cells affected. Such functional changes drive distinct network deficits which all converge on shallowing of Hippocampal attractors and hence disorganizing cognitive maps. Such disorganization is reflected in impaired sequential activity of Hippocampal place cells in offline and online states, which we propose drives thought disorder. Dashed lines indicate processes tentatively/indirectly implicated in schizophrenia. (HDAC: Histone Deacetylases, REST: repressor element-1 silencing transcription factor, SWRs: Sharp-wave ripples; PV: Parvalbumin).

Supplementary Information

Supplementary Discussion 1 - Shallow Attractors unify chemical hypotheses of schizophrenia

An account of schizophrenia as disorganized Hippocampal cognitive mapping provides a framework for relating multiple, seemingly competing transmitter-based theories of schizophrenia: the dopamine, GABA and glutamate hypotheses.

The dopamine hypothesis

It is widely accepted that dopamine dysfunction plays a role in schizophrenia¹⁰¹. Enhanced dopamine function is thought to underlie psychotic symptoms. While much of this has been attributed to the dopaminergic innervation of the basal ganglia via the nigrostriatal pathway, bidirectional interactions between dopaminergic cells in the ventral tegmental area (VTA) and the Hippocampus have also been implicated in the disease⁶⁷. Excessive activity in both the HPC and VTA may be part of a positive feedback loop where both structures mutually enhance, and dysregulate, each others' activity. Under **Prediction 2**, we discussed how Hippocampal dysfunction can drive the hyperdopaminergic state. Below we discuss how the hyperdopaminergic state could contribute to Hippocampal dysfunction.

Within this Hippocampus, dopamine is a key regulator of synaptic and network plasticity, particularly in relation to novelty or reward prediction errors¹⁰². Dopamine acting on D1-receptors enhances LTP and can alter Hippocampal spike timing dependent plasticity (STDP) rules, for example by reteroactively converting spike-timing dependent LTD to LTP¹⁰³. Increased tonic firing of DA afferents in schizophrenia may underlie aberrant salience¹⁰⁴, potentially by reducing the threshold for LTP induction and resulting in excessive, inappropriate associations. At the network level, dopamine has been shown to facilitate the stabilization of spatial maps¹⁰⁵ and goal-representations¹⁰⁶ in the Hippocampus, both of which are impaired in a mouse model of schizophrenia³². Dysregulated and excessive dopamine release may impair the selective stabilization of goal representations, giving rise to shallow attractors (Note that a recent study suggests that dopamine release via the Locus coeruleus may be critical for this effect)¹⁰⁷. Assessing the effect of dopamine receptor blockade, or optogenetic manipulation of dopaminergic afferents, on Hippocampal attractor dynamics in schizophrenia models would begin to address this hypothesis.

The GABA hypothesis

In addition to dysregulated dopamine, there is robust evidence to support an association between loss of Hippocampal interneurons and schizophrenia. Hippocampal interneuron deficits have been reported in schizophrenia patients^{44,108,109}, and ablation of NMDAR receptors in corticolimbic interneurons induces schizophrenia-like symptoms in mice.¹¹⁰ Moreover, as discussed above, the loss of parvalbumin interneurons in the DG has been implicated in pattern separation effects in schizophrenia. More generally, an impaired Excitatory inhibitory (EI) balance in the Hippocampus may underlie excessive associations in schizophrenia^{111,112}. Parvalbumin positive interneurons (PVNs), which receive converging input from principal neurons and in turn target the somatic and perisomatic compartments of such neurons, are critical for temporally organizing activity within a given neural assembly, and demarcating activity across assemblies(**Figure 2**)¹¹³. Disrupting such a process results in disorganized neural ensembles¹¹³ and may underlie disorganized maps in schizophrenia. Consistent with this, Belforte et al¹¹⁰ showed that knockout of NMDARs in cortico-limbic PVNs before 8 weeks, results in a schizophrenic phenotype (e.g. novelty induced hyperlocomotion) and the attenuation of gamma oscillations (However, see Bygrave et al 2016¹¹⁴ for confounding factors that suggest NMDAR hypofunction involves a multitude of neuron types). Moreover, Gamma oscillations, known to be deficient in SZ patients and models, are generated by a mechanism that involves feedback inhibition by fast-spiking PV interneurons (PVN)¹¹⁵. The importance of early disruption of these circuits and the role of PVN has also been highlighted in a recent study where schizophrenic behaviours (novel object recognition, sensory-motor gating in Paired pulse inhibition) in *PV-Cre; ErbB4^{fl/fl}* mice could be reversed by chemogenetic activation of PVN in the frontal association

cortex¹¹⁶. A similar mechanism may occur in the Hippocampus where impairments in PVN have been implicated in schizophrenic patients and mouse models. Indeed, post-mortem staining of schizophrenic brains have shown a reduction in Hippocampal PVN density compared to controls⁴⁴ (but see Woo et al ¹¹⁷) and more recent transcriptomics studies point to functional differences in neocortical PVNs amongst patients and controls¹¹⁸. These findings are consistent with loss/dysfunction of PVN mediating disorganized neuronal ensemble activity in schizophrenia. Direct evidence would entail testing whether Hippocampal neural ensembles encoding distinct memories are disorganized in schizophrenia in a manner that is dependent on PVN dysfunction.

The glutamate hypothesis

That NMDA receptor antagonists, such as phencyclidine (PCP), induce or exacerbate psychotic symptoms in humans has led to the glutamate hypothesis of schizophrenia^{119,120}. This has informed mechanistic animal studies, where PCP induces psychosis-like symptoms in rats and electrophysiology and immunostaining of brain slices showed changes in the amygdala and Hippocampus in rats after PCP application⁴⁶. In particular, NMDA receptor-dependent LTP is impaired in the CA1 of schizophrenia animal models^{45,46}. Deficits in LTP induction may underlie the inability to form stable attractors at goal locations in schizophrenia. Consistent with this, pharmacological blockade of NMDA receptors prevents overrepresentation of goals in area CA1 (**Figure 2**)⁷¹. However, this manipulation was systemic and would have affected NMDA-dependent processes throughout the brain, including those unrelated to LTP. A direct link between LTP deficits and goal overrepresentation in the Hippocampus would require, for example, depotentiating synapses potentiated during learning and observing a loss of goal overrepresentation ¹²¹. The relationship between plasticity and schizophrenia may be more complex, with enhancements in LTP also reported in schizophrenia models. For example, the schizophrenia associated DTNBP1 gene encodes Dysbindin protein that plays a role in the neuronal trafficking of proteins including receptors. In dysbindin-deficient mice, enhanced AMPAR responses and LTP were observed in CA3-CA1 Hippocampal synapses⁴⁷. Nevertheless, as discussed above, an enhanced potentiation (if it is not specific to neuronal inputs representing rewarded or salient states) may give rise to aberrant or dysregulated associations, which would result in the same net effect of shallowing attractors and disorganizing Hippocampal maps (**Figure 3**).

Overall, these findings suggest that dysregulated dopamine, compromised interneuron function and aberrant plasticity at glutamatergic synapses could all contribute to the shallowing of Hippocampal attractors underlying cognitive map function in the Hippocampus. This framing is useful in two ways. Firstly, it provides a unified framework for understanding the role of these distinct transmitter systems in schizophrenia. Secondly it provides a rationale for understanding the heterogeneity that famously characterizes the aetiology of schizophrenia. Multiple distinct pathways could achieve a similar end result: a shallow, disorganized cognitive map.

Supplementary Discussion 2 - Avenues for treatment

Our framework supports the following treatment paradigm:

1-In addition to schizophrenia patients, relatives of schizophrenics also score higher on thought disorder severity than non-psychiatric controls⁷⁴. Identifying mutations and epigenetic changes in Hippocampal plasticity-related genes that predispose individuals to disease not only allows identifying at-risk individuals and families, but also may allow more precise prediction of their probable disease progression and predisposition to thought disorder.

Example: Using model-based approaches to classify individuals as at risk of developing thought disorder based on the proximity of their genetic profiles to those of schizophrenia datasets associated with this symptom, guided by functional data linking such genes to shallowing of Hippocampal cognitive maps.

2-Point 1 above combined with understanding how epigenetic changes associated with early life events, such as traumatic life experiences, interact with genetic factors to elicit Hippocampal dysfunction can form the basis for precise, appropriately timed and personalized behavioural and drug-based interventions that prevent disease onset.

Example: molecular and environmental factors affecting early Hippocampal development (e.g. Plexins, exercise, trauma) could be targeted in at risk individuals.

3-Results showing mechanisms of symptom reversal in animal models provide hope for more precisely targeted post-hoc treatments when preventative measures fail.

Example: exercise¹²² and environmental enrichment^{116,123} can reverse schizophrenia symptoms in animal models by enhancing interneuron neurogenesis or function in the dentate gyrus respectively. This provides a mechanistic understanding of exercise-induced improvements in Hippocampal volume and short-term memory in schizophrenia patients¹²⁴. Our framework explains such an effect as a result of rescuing imbalance of PS/PC by enhancing the former, thereby promoting the formation of organized, deep cognitive maps. Combining such behavioural therapies with pharmacological treatments that target PV interneurons could provide a *robust* therapeutic strategy, especially for non-responders to dopaminergic treatments.

Supplementary Discussion 3 - Detailed Experimental Predictions

1-Impaired replay in schizophrenia is the result of “jumps” between Hippocampal sequences representing distinct memories: e.g., in schizophrenia mouse models experiencing two or more linear tracks, awake replay (in CA3 and CA1) in one track should exhibit non-random fragments of sequences from multiple tracks. (**Figure 1b**)

2-Jumps between sequences for distinct memories may correlate with enhanced performance on tasks that require associating distinct memories, but also should impair those that necessitate suppressing memory interference. This pattern should be seen in human patients at early or subclinical stages of the disease (e.g., at risk relatives of patients).

3-Molecular changes that impair pattern separation, enhance pattern completion or induce aberrant salience should have a similar end result of shallowing Hippocampal attractors in the CA3, causing jumps during awake replay (see point 1) and predisposing subjects to thought disorder (**Figure 3**). Functional grouping of genes based on their roles in deepening hippocampal attractors should allow a more accurate prediction of patient symptoms and prognosis than functional grouping based on lower level processes (e.g. LTP, interneuron function...etc).

4-Cognitive-mapping-related molecular changes outlined in point 3 should be enriched in Schizophrenia patients with a high degree of thought disorder compared to those with lower levels of thought disorder.

5-Molecular changes that give rise to either impaired LTP or enhanced yet dysregulated LTP at synapses onto CA1 (including CA3-CA1 and nucleus reuniens-CA1 synapses) should effectively result in a net shallowing of attractors towards goals relative to their surrounding regions - giving rise to impaired goal overrepresentation and goal-directed navigation. Where plasticity is enhanced, our framework predicts that this enhancement will exhibit little or no specificity for salient compared to non-salient stimuli. This may involve enhanced heterosynaptic plasticity, where synapses other than those exhibiting plasticity inducing patterns of activity are potentiated/depressed. Alternatively, this could involve a reduced threshold for homosynaptic plasticity, such that weak patterns of activity that typically don't induce plasticity at a given synaptic input in controls are effective in schizophrenic models.

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