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Active Inference, Epistemic Value, and Uncertainty in Conceptual Disorganization in First-Episode Schizophrenia

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***Background and Hypothesis*: Active inference has become an influential concept in psychopathology. We apply active inference to investigate conceptual disorganization in first-episode schizophrenia. We conceptualize speech production as a decision-making process affected by the latent "conceptual organization"—as a special case of uncertainty about the causes of sensory information. Uncertainty is both minimized via speech production—in which function words index conceptual organization in terms of analytic thinking—and tracked by a domain-general salience network. We hypothesize that analytic thinking depends on conceptual organization. Therefore, conceptual disorganization in schizophrenia would be both indexed by low conceptual organization and reflected in the effective connectivity within the salience network. *Study Design*: With 1-minute speech samples from a picture description task and resting state fMRI from 30 patients and 30 healthy subjects, we employed dynamic causal and probabilistic graphical models to investigate if the effective connectivity of the salience network underwrites conceptual organization. *Study Results*: Low analytic thinking scores index low conceptual organization which affects diagnostic status. The influence of the anterior insula on the anterior cingulate cortex and the self-inhibition within the anterior cingulate cortex are elevated given low conceptual organization (ie, conceptual disorganization). *Conclusions*: Conceptual organization, a construct that explains formal thought disorder, can be modeled in an active inference framework and studied in relation to putative neural substrates of disrupted language in schizophrenia. This provides a critical advance to move away from rating-scale scores to deeper constructs in the pursuit of the pathophysiology of formal thought disorder.**

Key words: thought disorder/bayes network/conceptual organization/free energy principle/dynamic causal models

Introduction

As clinicians and basic scientists work towards the age of *precision psychiatry*—broadly conceived as individualized biometrics[1] as well as estimates of computational parameters of behaviour[2–4]—we need tools to study hidden constructs of psychopathology. Such tools are essential for relating clinical symptoms and biological mechanisms. Active inference,[5] a formal theory of brain function, has moved us in this direction, contributing testable models of schizophrenia symptoms.[6–8] However, similar approaches are yet to be developed for features that some consider as more central to the construct of schizophrenia—Thought and Language Disorders (TLD)—which emerge as a distinct syndrome in factor analytical studies of symptoms with both positive and negative dimensions.[9,10]

In this work, we employ probabilistic modeling and active inference to (1) develop a computational approach to infer the elusive construct of *conceptual organization* that is said to underlie aberrant speech production and TLD in schizophrenia and (2) test the hypothesis that the salience network in the brain tracks conceptual (dis)organization seen in patients.

Previous literature on formal thought disorder has described the psychopathology of the aberrant mental state[11] or the linguistic elements expressed in this state.[12,13] Disrupted language is increasingly viewed as a biomarker that captures formal thought disorder.[14–19] We test a hypothesis about the mechanism underlying this disorder. Currently, conceptual disorganization refers to an observed symptom or sign. Here, it is used as a latent state.

Therefore, we focus on conceptual organization itself as a conditioning factor of disorganized speech in schizophrenia, being more consistent with the negative impact that such disorganization has on the real-world functioning of people with schizophrenia.[20]

Conceptual disorganization is indirectly measured via, for example, the P2 item of the Positive and Negative Syndrome Scale (PANSS)[21] and the thought language index (TLI)[22].[20] Thus, it is a disturbance in the process of thinking[21–23] inferred from verbal behavior. For example, in the TLI (figure 1) patients describe pictures in 1-minute speech trials, and raters score the productions looking for evidence of disordered thought.

Recently, we applied a computational linguistic tool to speech samples collected using the TLI and reported that global impoverishment of thinking and PANSS P2 scores negatively correlated with a psychological dimension referred to as *analytic thinking*.[14] Analytic thinking scores track knowledge organization; it is computed from the proportional use of function words (eg, prepositions, articles, and pronouns).[24] Although the score indexes knowledge organization, its association with conceptual organization has not been investigated and continues to be an indirect measure of an unobservable psychological state. In this work, we furnish this psychological dimension with a formal model of conceptual organization. Briefly, conceptual organization (and by extension conceptual disorganization) can be expressed as *epistemic value*: A quantity that indicates the decreased uncertainty expected given a speech production.

Our theory leads to predict where in the brain the between-groups variability in conceptual organization (estimated from analytic thinking scores) can be tracked. Subsequently, we hypothesize that conceptual disorganization in schizophrenia patients affects the effective connectivity between the anterior cingulate cortex (ACC) and the anterior insula (AI) within the salience network—functionally specialized in encoding uncertainty. Because we focus on conceptual organization as a latent factor,[25] an introduction of active inference contextualized in language production is required to conceive this factor.

A Primer on Active Inference in Conceptual Organization

In active inference, the brain embodies a *generative* model encoding beliefs about the (hidden) environmental causes of sensory information. The organism has uncertainty about the reliability of its beliefs and reduces this uncertainty by updating the model via perception and action. Formally, uncertainty reduction takes the form of free energy minimization.[26–28] In this section, we describe a toy example about how active inference explains the way language production, as a special case of action, minimizes free energy. The example is highly idealized, yet it shows the underlying mathematical principles required for the formal operationalization.[29]

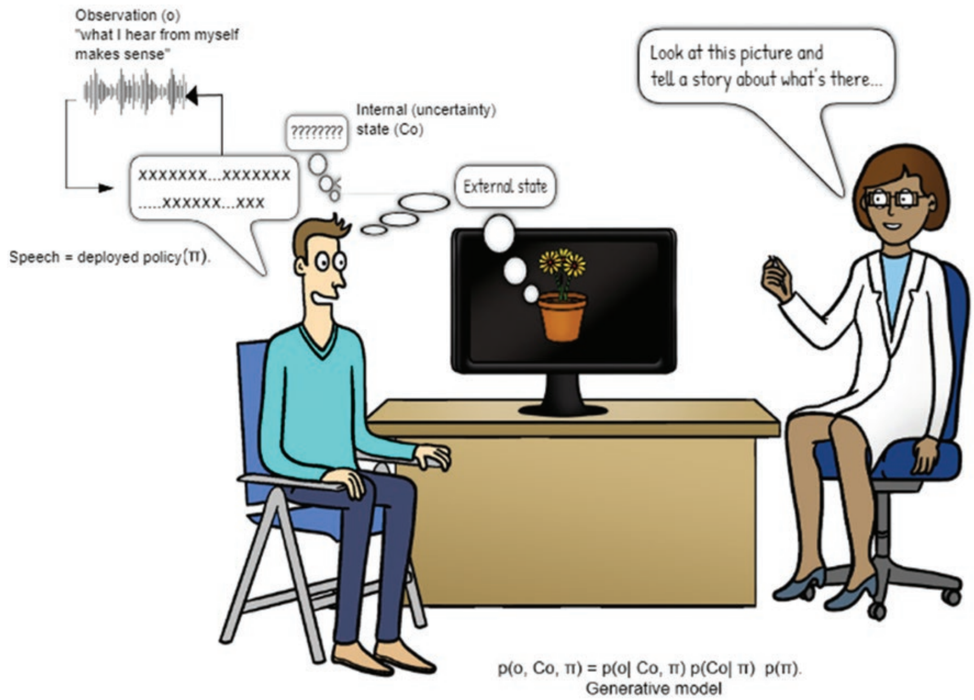

Fig. 1. A cartoon summary of the generative model of speech production during the TLI interview. Although there is a degree of communication with another person, the interview used in this study focuses on the ideational function of language, to make sense of our external world, actualizing its epistemic property. Figure created with Toonytools (classic.toonytools.com).

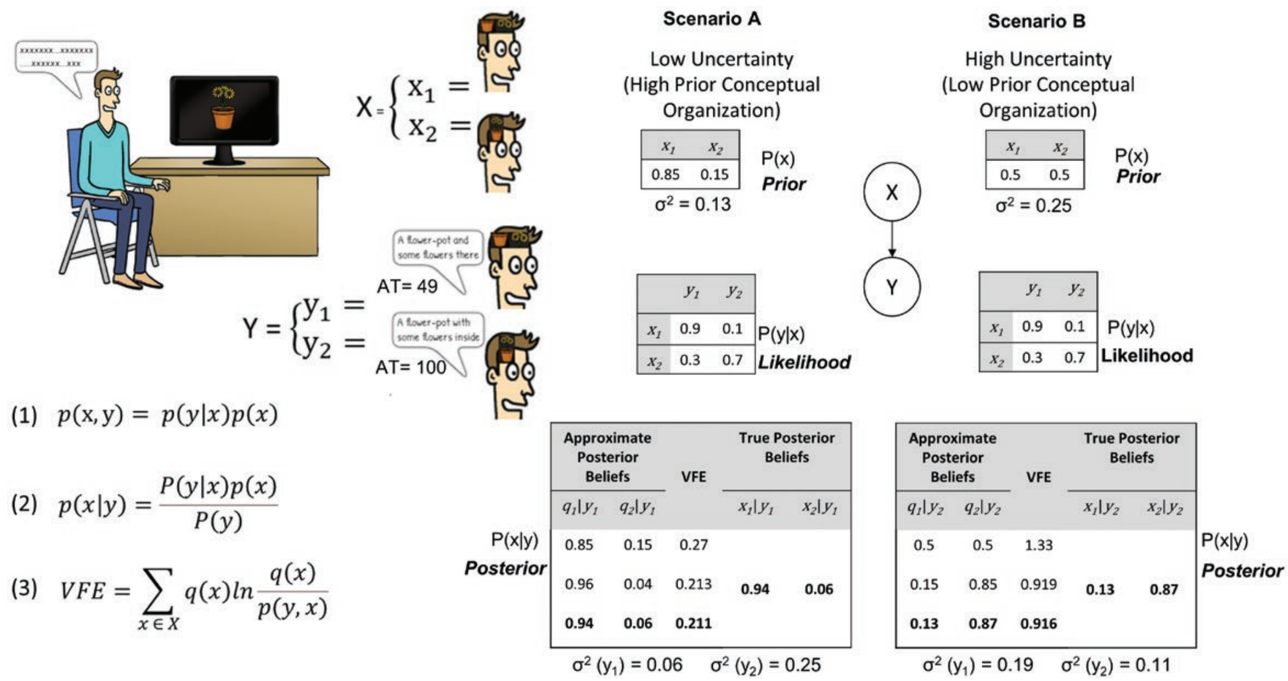

Fig. 2. Toy example of variational free energy minimization during language production. The agent intents to make sense of a picture via their embodied generative model (equation 1). In 2 scenarios (high, A, and low, B, uncertainty), the agent brings to the table the same pair of possible (prior) representations (3D images) of the world with relevant prior probabilities, P(x), and prior uncertainty (σ^2). To reduce the uncertainty, the agent speaks aloud and hears their own utterances. Hearing 2 different productions (with different analytic thinking scores, At) would differentially minimize the uncertainty (ie, VFE). However, hearing the same utterance with high At (y_1) would lead to a more substantial minimization ($\sigma^2 = 0.06$) in the scenario with a low prior uncertainty, $\sigma^2 = 0.13$ (ie, high prior conceptual organization). In this example, the posterior beliefs (uncertainty or conceptual organization) can be computed directly from equation 2. However, p(y) is intractable in real situations. Instead, posteriors are found via VFE minimization (equation 3)—testing different approximate posteriors, q, until converging with the true posterior. Figure created with Toonytools (classic.toonytools.com).

The simplest generative model comprises a joint distribution over prior beliefs (x) and sensory data (y) that factorizes as $P(x,y) = P(y|x)\ P(x)$. A graph encoding this representation (figure 2) indicates that the sensory information depends on the agent's beliefs about the world. The agent updates their *prior* into *posterior beliefs* given the sensory data. This happens via free energy minimization which, mathematically, plays the same role as any other quantity minimization (eg, minimization of least squared errors in regression analysis) but using approximate posterior distributions, q(x). During speech production, the set of sound waves constitutes one source of sensory data which an agent leverages to update their prior beliefs. In other words, we update our beliefs—and decrease the uncertainty about the world—by perceiving the results of our own actions (eg, hearing our own speech when talking about our environment).

To grasp how language production minimizes uncertainty, consider an agent describing a picture of pots and flowers (figure 2). In scenario "A," it is highly likely (eg, $P = .85$) that the agent holds a visual representation (Supplementary Materials) of flowers inside the pot, their prior conceptual organization about the scene. There is some uncertainty (the variance of the distribution) in this conceptual organization, $\sigma^2 = P(1-P) = 0.85 \times 0.15 = 0.13$. However, by verbally describing the scene the agent updates their conceptual organization, changing the uncertainty. For example, the agent can be lowly analytical and say that "there is a flower-pot and some flowers there" (analytic thinking score ≈ 50), leading to an increase in the uncertainty (44.7 vs 55.3, $\sigma^2 = 0.25$). Conversely, they can be highly analytical by saying that "there is a flower-pot with flowers inside" (analytic thinking score = 100), leading to a decrease in uncertainty (0.94 vs 0.06, $\sigma^2 = 0.06$). Now consider the scenario "B" in which the prior conceptual organization about the scene is highly uncertain (eg, 50 % vs 50%, $\sigma^2 = 0.25$), the verbal description with the highest analytic thinking score would yield a smaller decrease in uncertainty (75% vs 25%, $\sigma^2 = 0.19$). This example indicates that how much uncertainty decreases via language production depends on both the sequence of words we select and the level of uncertainty embodied as our prior conceptual organization.

The Active Inference of Conceptual Organization in the TLI Interview

We mentioned that to decrease uncertainty the speaker selects a sequence of words. However, the selection of words itself is not what matters to minimize free energy.

It is the actual production of the words the important factor because in doing so the agent changes their perceptions. This entails that we ascribe not only a communicative but also a representational (ideational) function to language.[30] Previous active inference works have targeted the communicative function—in which variational free energy is reduced when the agent perceives a message (eg, the answer to a question from a conversational partner[31–34]). However, the agent can also engage in the ideational function (to represent their external world[30]), variational free energy would decrease by perceiving their own speech. In this context, because the agent can select many different combinations of words to "organize their representation of the world" they estimate beforehand (during the selection process) the expected free energy that would be minimized, calling in a decision-making process.[35]

Decision-making implies estimating the free energy that would be minimized if a sequence of actions—a policy—were deployed. In the TLI interview, the agent explores which combination of function and content words would minimize the uncertainty in their prior conceptual organization. While the generative model we introduced in the toy example included the effect of perceiving our own speech *after it has been produced*, a generative model of language production as a decision-making process like in the TLI interview entails a joint distribution over (policies, π; states, eg, conceptual organization (Co); and observations, o) factorized as: $P(\mathrm{o}, \mathrm{Co}, \pi) = p(\mathrm{o}|\ \mathrm{Co}, \pi)\ P(\mathrm{Co}|\ \pi)\ p(\pi)$ and upon which the agent estimates the amount of uncertainty (epistemic quantity) that a given policy would decrease if deployed (Supplementary Materials). In what follows, we will focus on policies associated with producing the speech that minimizes uncertainty and how it relates to analytic thinking.

Minimizing Uncertainty for Analytic Thinking During Speech Production

We regard speech production as a partially observable Markov decision process (POMDP,[36] figure 3) that yields a stream of words produced one after another. At each timestep, the agent can, for example, choose either a content word from a pool (eg, their lexicon) or a function word. The produced word at time t depends on the conceptual organization at time t-1. We assume that these states represent the current and previous states of conceptual organization, a state factor that can take 2 values: *high organization* and *low organization* (ie, disorganization).

The outcome of the decision process would be a chosen discourse that would maximize the epistemic value, minimizing the *uncertainty*. However, in the decision process, the conceptual-organization state at $t = 0$ should be defined a priori which in the TLI interview would correspond to the prior conceptual organization state with which the patient begins a trial.

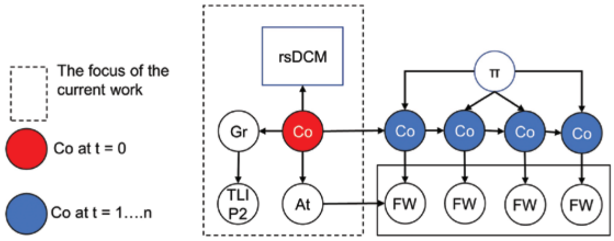

Fig. 3. Active inference and probabilistic graphical model of the POMDP of speech production in the TLI interview. The subgraph (dashed rectangle) allows us to estimate the distribution of Co over groups at $t = 0$. At (analytic thinking score), Co (conceptual organization), rsDCM (DCM set of parameters of resting state fMRI), FW (function word), π (Policy -ie, a stream of words), *TLI (Thought Language Index scores), P2 (Item P2 representing clinician-rated Conceptual Disorganization score from the Positive and Negative Syndrome Scale PANSS), both providing clinical symptoms scores*, Gr (group).

Hypotheses

We evaluate 2 hypotheses that follow on the formal principles presented above. First, because a produced word in a speech sample at time = t depends on the conceptual organization state at time = $t-1$, and this state is an index of reduced uncertainty, then the analytic thinking scores must depend on the conceptual organization state—being lower in first-episode schizophrenia (FES) than in healthy control (HC) subjects.

Second, cognitive tasks under uncertainty elicit activity in (at least) ACC and AI nodes of the salience network—which appears to track uncertainty in a supramodal and task-independent manner[37–41] thus being congruent with the proposal that uncertainty is an internal state that affects all aspects of cognition and decision making[26,27] (ie, a domain-general factor). Interestingly, different perspectives have shown a role of the salience network in the generation of disorganized speech and behavior in psychosis despite not establishing a formal link between conceptual organization and uncertainty.[42–49] Therefore, the prior level of conceptual organization—as a special case of uncertainty—of schizophrenia patients and healthy controls would differentially affect the effective connectivity between the ACC and the AI. This approach shifts the focus of the neural basis of 'thought disorder" from language networks to the general domain of social decisions.[50]

Methods

Subjects

This study pursues one of the pre-registered objectives of the observational study TOPSY (NCT02882204). Data from 30 FES (6 females) and 30 HC (12 females) subjects were analyzed (Supplementary Materials). Participants provided written informed consent conforming to the regulations of the Western University Health Sciences Research Ethics Board, London, Ontario, Canada.

Patients were in the acute phase of illness and recruited upon referral (irrespective of hospitalization status and before antipsychotic treatment was established) from the Prevention and Early Intervention for Psychosis Program (PEPP) at London Health Sciences Center, London, Ontario, Canada between April 2017 and July 2019. Based on the best estimate procedure[51] and the Structured Clinical Interview for DSM-5,[52] they received a 6-month consensus diagnosis from a minimum of 3 psychiatrists, confirming that patients did not meet the criteria for bipolar disorder with psychotic features, a major depressive disorder with psychotic features, or drug-induced psychoses. HC subjects were recruited from the community through posters. They had neither personal history of mental illness nor a family history of psychotic disorders. None of the participants met the criteria for substance-use disorder in the past year according to DSM-5 criteria,[52] had a history of a major head injury. Participants did not report a history of uncontrolled medical illness, the presence of intellectual/developmental disorder, or lifetime antipsychotic exposure longer than 2 weeks of lifetime antipsychotic exposure.

Resting-State fMRI and Dynamic Causal Model

Participants underwent a resting-state fMRI inside a MAGNETOM Plus 7T MRI scanner (Siemens Corp., Erlangen, Germany) located at the Center for Functional and Metabolic Mapping of Wester University. We estimated the effective connectivity within the ACC-AI network (Supplementary Materials). At a subject level, we inferred the unobserved neural activity of coupled neuronal populations between the 2 regions fitting a dynamic causal model[53] to the fMRI time-series (rsDCM). Our DCM represented both intrinsic or within-region (GABAergic) and extrinsic (between-region) glutamatergic connections.[53–55]

Probabilistic Graphical Models

At a group level, we estimated the conditioning effect of a prior conceptual organization (Co, at $t = 0$) on the connectivity within the ACC-AI encoded in a subgraph representing the joint distribution of (Co, analytic thinking, symptoms of disorganization, group, and rsDCM parameters). We first estimated the marginal distribution of Co, the probability of group membership given Co, and the probability of analytic thinking given Co (M1). To demonstrate the dependency between Co and analytic thinking, we compared this graph against a graph (M2) with unconnected nodes (figure 4). The estimated marginal distribution of Co was set as the prior of a model leading to inferring the posteriors of the effective connectivity parameters given Co (figure 5). The model included clinically rated TLD metrics (PANSS-P2, global disorganization of thinking, GDIT, and global impoverishment of thinking, GIOT) conditional upon group. These metrics were included to test two alternative hypotheses.

To test whether the 2-node network encodes Co, we compared this model (M1) against two competing models (M2 and M3). In M2, Co would influence neither the connectivity of the salience network nor the observed TLD. In M3, analytic thinking would explain the connectivity of the salience network as well as the clinical ratings, without a necessity to invoke the latent Co. Bayesian information criterion numbers were used to select the winning model. Parameters estimates were subjected to independent sample *t*-tests (Bonferroni correction $P < .0125$) for between-groups comparison.

Results

The Analytic Thinking Score Causally Depends on Unobserved Prior Co

The two competing networks shown in figure 4 represent analytic thinking, Co, and group. However, the network in which Co affects both analytic thinking score and group outperformed the alternative network. The estimated marginal distribution of Co was $P = .58$ (low Co) and $P = .42$ (high Co). The distribution of Co given group indicates that FES explains low Co ($P = .9$). High Co is more likely in HC subjects ($P = .74$).

High and low Co cause high and low analytic thinking ($M = 79.3$, $Sd = 9.02$; $M = 50.6$, $Sd = 15.8$, respectively; means difference = −28.7; 95% CI [−35.3, −22.1]; $t_{(58)} = 8.64$; $P < .0001$). Lower analytic thinking were seen in schizophrenia compared to healthy subjects (means difference = −18.5; 95% CI [−27.4, −9.6]; $t_{(58)} = 4.18$; $P < .0001$)—reproducing our previous results.[14]

The Effective Connectivity Between the ACC and the AI Encodes the Probability Distribution of Prior Conceptual Organization

Figure 5 shows that the Bayesian network in which the rsDCM parameters depend on conceptual organization outperformed the competing models. Figure 6 shows that if a subject had low Co (at $t = 0$) the influence of the AI on the ACC would be stronger than if they had high Co (means difference = 0.09, [0.08, 0.1], $t_{(58)} = 15.69$, $P < .0001$). Furthermore, if a subject had low Co self-inhibition within the ACC would be stronger than if they had high Co (means difference = 3.8, [3.34, 4.26], $t_{(58)} = 16.54$, $P < .0001$). The influence of the ACC on the AI did not vary between conceptual organization states (means difference = 0, [0.0, 0.0], $t_{(58)} < 0.001$ 0, $P < .99$). Finally, if a subject had high Co self-inhibitory connections within the insula would be stronger than if they had low Co (means difference = 1.16, [0.1, 2.2], $t_{(58)} = 2.22$, $P = .03$). However, this difference did not survive correction.

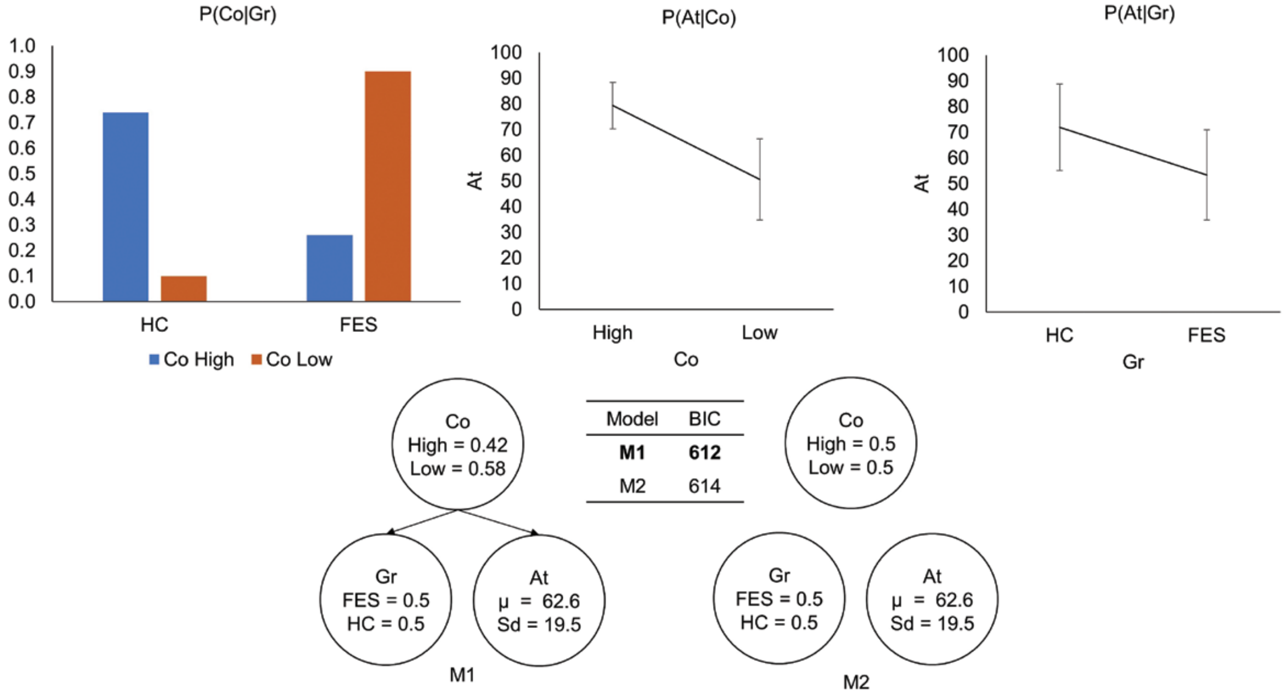

Fig. 4. Bayes networks testing the hypothesis that the analytic thinking score is causally associated with the unobserved Co. The bar graph shows the Co posteriors given group. The middle and right line graphs show the posteriors (mu and standard deviation—error bars) of analytic thinking given Co and group (Gr) respectively. Estimated distribution of Co in M1 (low = 0.58, high = 0.42) were set as priors in the generative model of figure 5. Probability values inside nodes are priors.

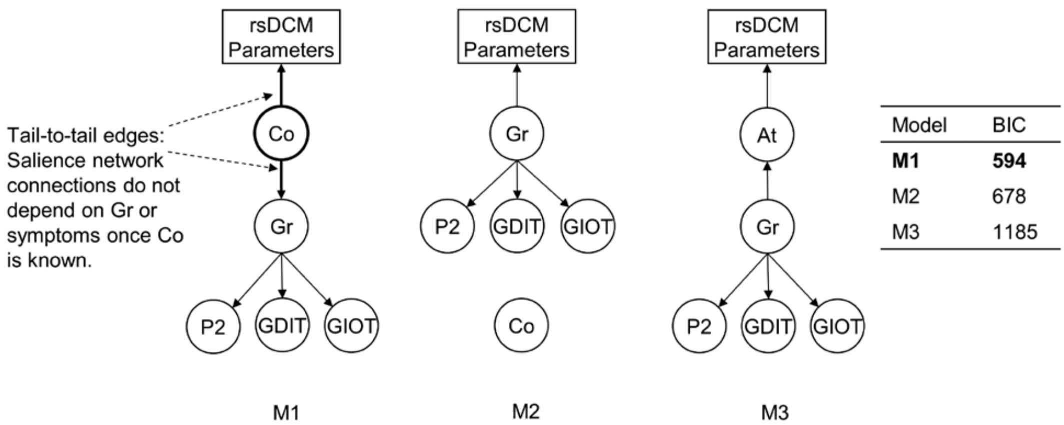

Fig. 5. Bayes networks testing the hypothesis that the effective connectivity parameters of resting state fMRI of the salience networks encode Co. M2 explaining group differences and rsDCM parameters in terms of differences in rating scales underperformed M1 explaining those differences in terms of conceptual organization. Tail-to-tail edges in the Co (conceptual organization) node indicate that after knowing the Co state rating-scale scores or group membership does not add anything about the effective connectivity of the salience network.

Discussion

We report 2 major findings. First, in FES, prior conceptual disorganization (ie, low conceptual organization) causes low analytic thinking in speech samples produced during a TLI interview. Second, effective connectivity within the salience network (ACC and AI) encodes conceptual organization states. We suggest that conceptual organization influences both the diagnostic status and analytical thinking in psychosis, with reduced conceptual organization binding clinical measures of thought disorder to the network's effective connectivity. Reduced conceptual organization causing a low analytic thinking score in the FES group speaks to a low epistemic value that patients assigned to the expected free energy minimization when deciding for the deploy speech.

We collected fMRI data at rest and not during speech production to test the hypothesis that the salience network's connectivity is associated with the conceptual

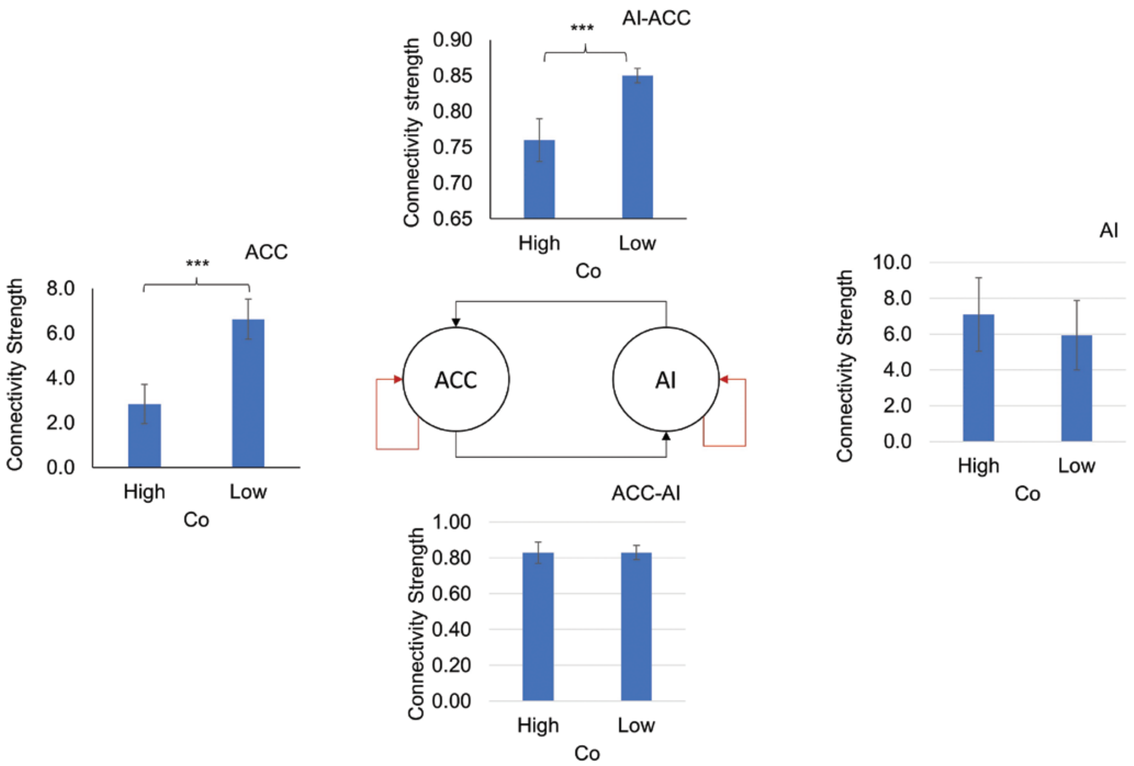

Fig. 6. Probability distributions of effective connectivity parameters conditional upon conceptual organization (Co) level. *** $P < .0001$.

organization. This design is viable as we assume, under POMDP, that conceptual organization represents the current state into which past states are implicit. Analytic thinking relates to conceptual organization at $t = 0$ which in turn relates to effective connectivity. Once the distribution is estimated, the POMDP comes to play, wherein the subject's preferred observations (perceived speech) are those that maintain the high-probability states of the continuously existing conceptual organization.

Based on the semantics of Bayesian networks, given a particular conceptual organization state group membership becomes independent of the analytic thinking score, and vice versa. This fact allows us to constrain the conditional distribution of group membership while ignoring the marginal distribution of analytic thinking when specifying the model comprising connectivity parameters. Furthermore, when the formalisms are applied to psychopathology, we can realize that diagnostic probability, as well as symptom/sign ratings, are consequences of a latent psychopathology which in turn is a consequence of latent pathophysiological processes.

Symptom scores are obtained from rating-scale metrics, but more objective measures from computational linguistics such as analytic thinking scores can be treated similarly in generative models of psychopathology. By demonstrating that the winning model linking diagnostic probability with observed ratings involves the latent construct of conceptual disorganization (figure 4) and this construct links the pathophysiology of a brain network-level dysconnectivity with the clinical expression (ie, diagnostic and symptom rating probability; figure 5), we provide a generative nosological model for TLD that typify schizophrenia.

Mapping the Marginal Posterior Distribution of Hidden Conceptual Organization on the Brain

Despite being correlated with positive and negative symptoms,[56] speech disorders have been treated in previous works as a domain-specific set of symptoms.[17,19,57] Here, conceptual disorganization is a special case of domain-general uncertainty that also influences the overall diagnostic probability, ie, binding together positive and negative symptoms as per the prevailing construct.[7] Based on this role of uncertainty in brain function and dysfunction, we mapped conceptual organization onto the salience network. This does not mean that this network is isolated from the rest of the brain in its influence on the conceptual organization.

The effective connectivity between the ACC and AI summarizes outer messages conditional on specific dependencies.[58–60] Nodes are functionally specialized to represent states, observations, and policies. Furthermore, nodes are functionally integrated to compute the posteriors. In terms of a probabilistic graph, the communication between ACC and AI is represented by the precision of the posterior probability of the conceptual organization state given a policy. This precision seems to be affected by an increase in self-inhibitory activity in the ACC and an increase in excitatory activity from the AI to the ACC—given a low conceptual organization state in FES. Applying previous interpretations of DCM models,[61] one can infer affected "synaptic gain control" within the ACC with an increased excitatory drive from the AI to ACC in low conceptual organization state. In other words, the message passed from the AI to the ACC and the increased self-inhibitory activity within the ACC "would conspire" against the decision-making process during word selection.

Strengths, Limitations, and Future Work

The current work has 2 additional strengths. First, FES data were collected from subjects with minimal anti-psychotic use and that experienced a first episode of psychosis. Therefore, the effect of chronicity and psycho-pharmacological treatment were minimized. Second, to quantify the same latent construct we used not only an objective score (analytic thinking) but also 2 symptom ratings (TLI and PANSS-P2 scores) obtained from 2-time points.

Our prior work oriented the selection of the NLP variable related to Thought and Language Disorder of psychosis; other alternatives may better reflect conceptual organization. But our modeling goal required the use of a quantifiable variable reflecting language disorder, analytic thinking scores served this purpose.

We estimated conceptual organization states at $t = 0$. In future work, we will fit the PODMP to speech samples which will allow us to quantify the epistemic value in terms of expected free energy. In this pursuit, a limitation of the current work should be addressed. The analytic thinking score neglects the effect of content words. A complete approach should include syntax and semantics. Furthermore, "resting state" is in essence an unconstrained mental state. Thus, a systematic bias due to across-group differential mental processes cannot be ruled out, though this was minimized by a consistent set of instructions and limiting the overall duration of the rest.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Author Contributions

RL provided the theoretical framework, the hypotheses, modeling, and took the lead in writing the first draft of the manuscript. AS contributed to the first draft of the manuscript. AS and SF performed speech data processing, MM collected the data and assisted in analysis. LP sourced funding, assessed patients, supervised symptom ratings, designed and coordinated the project and reviewed and edited the manuscript.

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