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Current Opinion in Neurobiology

Can circular inference relate the neuropathological and behavioral aspects of schizophrenia?

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Schizophrenia is a complex and heterogeneous mental disorder, and researchers have only recently begun to understand its neuropathology. However, since the time of Kraepelin and Bleuler, much information has been accumulated regarding the behavioral abnormalities usually encountered in patients suffering from schizophrenia. Despite recent progress, how the latter are caused by the former is still debated. Here, we argue that circular inference, a computational framework proposed as a potential explanation for various schizophrenia symptoms, could help end this debate. Based on Marr's three levels of analysis, we discuss how impairments in local and more global neural circuits could generate aberrant beliefs, with far-ranging consequences from probabilistic decision making to high-level visual perception in conditions of ambiguity. Interestingly, the circular inference framework appears to be compatible with a variety of pathophysiological theories of schizophrenia while simulating the behavioral symptoms.

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Current Opinion in Neurobiology 2017, **46**:154–161

This review comes from a themed issue on **Computational neuroscience**

Edited by **Adrienne Fairhall** and **Christian Machens**

http://dx.doi.org/10.1016/j.conb.2017.08.012

Introduction

We live in an ambiguous and constantly evolving environment. Being able to make sense and act in such an uncertain world is fundamental for our survival. Consequently, one would expect our brain to be equipped with mechanisms capable of representing and using this uncertainty to draw valid conclusions. Indeed, today there is substantial evidence that various cognitive and motor tasks are probabilistic in nature [1–3], and many of these tasks are performed by humans almost optimally [4,5]. At the same time, scientists have become more and more interested in tasks in which human performance is suboptimal [6,7], which could be due to the use of wrong information or the use of approximations. More recently, this type of impaired inference has been theorized to be at the roots of various neurological or mental disorders, including schizophrenia (cf. Box 1) [8•,9,10].

In this review, we focus on a particular framework for schizophrenia, called *circular inference* [10,17,18••]. In the first part, we discuss important computational and algorithmic aspects of the framework and its relevance to perception and cognition. In the second part, we propose potential neural and anatomical implementations of the framework and draw connections with other well established neurobiological models of schizophrenia [19,20].

The computational level: the Bayesian formalism

When we look at the face of a person, we instantly perceive it as three dimensional since we have depth perception. Although that might seem like a trivial task, which is executed by the brain in a few msec with amazing accuracy, the truth is very different. The 3D shape of a face has to be inferred from the ambiguous 2D retinal projection, using only the inconclusive visual information and prior knowledge accumulated from the past. The optimal integration of such ambiguous information can be formalized using the Bayes theorem:

$$P(Y|X) = \frac{P(X|Y)P(Y)}{P(X)}$$

where Y and X are random variables (continuous or discrete) representing the 3D interpretation and the 2D retinal image, respectively; $P(Y|X)$ is the posterior probability representing our subjective belief about the 3D interpretation after receiving the new sensory evidence; $P(Y)$ is the prior or our subjective belief before the new evidence; $P(X|Y)$ is the likelihood function that formalizes the dependence of the sensory evidence on the 3D interpretation; and finally $P(X)$ is a normalization term that ensures that the posterior is a probability distribution summing to 1.

From such a perspective, visual perception can be seen as the process of guessing the most probable cause (e.g., 3D object) of the sensory evidence (e.g., 2D retinal image)

Box 1 The schizophrenia spectrum

Schizophrenia is a common mental disorder (approximately 1% lifetime prevalence), with a heterogeneous genetic and neurobiological background, that may clinically result in some combination of positive symptoms (i.e., features that are not normally present, such as *hallucinations*, *delusions or disorganized thinking*), negative symptoms (i.e., characterized by the absence of normal functions, such as *social withdrawal or affective flattening*) and a broad set of cognitive dysfunctions [11]. A unique molecular process/cognitive domain appears unlikely to be involved in schizophrenia, and among the various pathophysiological models proposed to account for this complex phenotype, a widespread change in the neural balance of excitation/inhibition has received multiscale support [12•]. The main findings in schizophrenia are: (i) the reduction in the GABA-synthesizing enzyme GAD-67 measured in post-mortem tissue [13]; (ii) abnormalities in Delta/Gamma/Theta band oscillations [14]; (iii) the effectiveness of $D2_R$ antagonists on psychotic symptoms [15], suggesting a dopamine hyperfunction (at least in the mesolimbic pathway); and (iv) the similarity in clinical manifestations after administering $NMDA_R$ antagonists to healthy volunteers [16], suggesting $NMDA_R$ hypofunction.

[21]. For the guess to be optimal (at least for Gaussian variables), likelihood and prior knowledge have to be weighted by their precision, which corresponds to the inverse of the variance of the respective probability distributions. If the information is very precise, then its relative contribution becomes larger.

The algorithmic level: belief propagation and circularity

In real life, most of the decision-making problems, perceptual or not, that we have to solve depend on many variables. In many cases, finding the posterior probability of those variables is not an easy task, as it might need calculation of intractable integrals or simply a huge number of summations, which increases exponentially with the number of variables. This problem can be solved by using a generative model, which is a hierarchical representation of the causal structure of the world. A generative model consists of nodes, representing variables, and edges, representing conditional dependencies. Nodes can be arranged in a hierarchical way such that variables in one layer are potential causes of the variables in the layer below (cf. Figure 1a).

A very general, powerful and efficient algorithm to perform inference in such a generative model is belief propagation (i.e., the sum-product algorithm, [22]). In belief propagation, sensory information S (in Figure 1a, this corresponds to the probability of a leaf being present, based only on sensory information) climbs the hierarchy in a feedforward way (bottom-up processing) and at the same time, prior information P (e.g., probability of being in a forest, before receiving any sensory information) moves downward as feedback (top-down processing). Then, each node calculates a belief for the underlying variable (equivalent to the posterior, e.g., $P(X_{tree}|S)$) and sends local messages (e.g., $M_{tree\rightarrow leave} = P(X_{leaf}|X_{tree})$) to all the neighboring nodes. As a result, information, in the form of beliefs, is propagated throughout the system.

If we assume binary variables and use the log-ratios of the probabilities, then beliefs and messages can be calculated by the following recursive equations [10]:

$$M_{ij}^{t+1} = W_{ij}(B_i^t - M_{ji}^t)$$

$$B_i^{t+1} = \sum_j M_{ji}^{t+1}$$

where M_{ij}^t is the message from node i to node j in time t, B_i^t is the belief of node i at time t, and $W_{ij}(B)$ is a sigmoid function of B.

The second equation simply means that each node calculates a belief by summing the messages coming from all its neighbors (e.g., the belief about the presence of a tree is equal to the sum of the messages from the forest and the leaf nodes). The first equation, on the other hand, means that the message travelling from node (i) to node (j) (e.g., from forest to tree) is a function of the belief of the sending node (i) (in our e.g., the forest), after we subtract the effect that the receiving node (j) has on the sending node (i) (e.g., message from tree to forest).

This correction is crucial. Without it, the algorithm would produce loops, that is, reverberations of bottom-up and/or top-down information. In such 'loopy' belief propagation, the consequences are treated as causes and vice-versa, and the information in the upward and the downward stream can be mixed and overcounted. As a result, beliefs can take extreme values (e.g., absolute certainty) and the system becomes overconfident (Figure 3, see also the section on '*Behavioral correlates*'). In other cases, beliefs can be reversed (to believe that something is present when there is nothing, i.e., having an aberrant perceptual belief or hallucinations) or start oscillating (i.e., a phenomenon called *frustrated network*). Recently, this kind of circular propagation of information in cortical and subcortical networks of the brain has been suggested to underlie the positive and possibly the negative and disorganized symptoms of schizophrenia [18••]. In the next section, we will describe the possible neural and anatomical implementations of belief propagation in the brain, and we will discuss how *circular inference* might be associated with well-known physiological and anatomical impairments in schizophrenia.

The neural level: implementing inhibitory loops

Currently, the brain is commonly considered a hierarchical system [23,24]. Many algorithms could be used by such a system to make probabilistic inferences [22]. Again, among the many suggestions, belief propagation