A number of empirical studies provide support for these model predictions (e.g., Barch et al. 2003; Cohen et al. 1999b; Javitt et al. 2000; Servan-Schreiber et al. 1996; Stratta et al. 1998). However, it is not clear from the level of description provided by P&S whether their theory would also predict that such factors should influence the severity of cognitive deficits in schizophrenia. It is also possible that simulations of specific cognitive tasks in the P&S framework would identify other conditions that are especially dependent on their proposed NMDA-receptor mechanism. In our experience we have found that the process of simulating empirical phenomena forced us to refine and elaborate our initial conceptual hypotheses in ways that we could not have predicted ahead of time.

In summary, we are intrigued by the theory put forth by P&S and encourage the authors to take this theory to the next level by providing an explicit computational implementation that can be compared with competing theories.

A wide-spectrum coordination model of schizophrenia

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Abstract: The target article presents a model for schizophrenia extending four levels of abstraction: molecules, cells, cognition, and syndrome. An important notion in the model is that of coordination, applicable to both the level of cells and of cognition. The molecular level provides an "implementation" of the coordination at the cellular level, which in turn underlies the coordination at the cognitive level, giving rise to the clinical symptoms.

The model of schizophrenia presented by Phillips & Silverstein (P&S) can be depicted as follows:

$$\text{NMDA}\downarrow \Rightarrow \text{neur. coord.}\downarrow \Rightarrow \text{cogn. coord.}\downarrow \Rightarrow \text{schiz.}\uparrow$$

This requires some explanation from the following dictionary:

NMDA	N-methyl-D-aspertate glutamate receptor activity
neur. coord.	neuronal coordination
cogn. coord.	cognitive coordination
schiz.	schizophrenia symptoms
$X\downarrow$	*X* decreases
$X\uparrow$	*X* increases

In somewhat more detailed terms, the model states the following. If the activity of NMDA glutamate receptors in the cortex is below normal, then neural coordination within and between cortical regions is decreased; this in turn implies decreased cognitive coordination, such as disambiguation and dynamic grouping; this then will be the direct cause of the symptoms of schizophrenia, such as impairments of perception, preattentive sensory gating, selective attention, working memory, and long-term memory. The authors choose to focus on disorganization.

The way the authors come to their model is as follows: NMDA-antagonists cause schizophrenia-like symptoms; schizophrenia implies impaired cognitive coordination, and vice versa; neural coordination is behind cognitive coordination. The model postulates that the NMDA glutamate channels provide a control for the neural coordination. The rationale behind this is that the NMDA-receptors are voltage-gated, that is, they depend on both the ligand and the right voltage to be opened. So they may indeed be used to coordinate processes (they essentially have the function of an AND-gate in a computer).

One virtue of the model is that it is *wide-spectrum.* It ranges from a molecular mechanism via cellular phenomena, via cognition, to psychiatric symptoms. The model makes predictions about patients suffering from schizophrenia: There is impairment of global, but not local, motion perception; high frequency rhythms (gamma) will be reduced. This implies that the model is falsifiable.

The main virtue of P&S's model is its emphasis on coordination, interaction. In computer science, a notion and theory has emerged that seems relevant here: that is, the notion and theory of communicating systems (see Milner 1999). Although everything happening in a computer may be described by fluctuating bits, the theory of communication forms a convenient level of abstraction. Some bits encode meaningful information to be used later, other bits represent actions that are relevant at the very moment. An interacting communication, the most fundamental concept in the mentioned theory, needs two half-acts, each waiting for the other half to be present simultaneously (like two persons who want to shake hands).[1] All this may be useful for a thorough theoretical underpinning of the way in which coordination is implemented by NMDA glutamate channels.

Although a single model for schizophrenia is presented, this does not imply that it is a homogeneous condition. For, there are many ways in which coordination can be impaired. Also, the effects can vary in severity. The authors give several examples of this and it is also apparent from the computer science theory of communicating systems, mentioned above.

The authors mention how their model is similar to many other theories, though not in all aspects. The theories they put forward regarding the cause of the disconnection between cortical regions are mainly similar to each other, apart from the fact that they do not speak about coordination *within* regions and focus on long term, that is, learning, effects (see Dolan et al. 1999; Friston 1999). P&S do focus in their model on the cortex but mention that other brain regions will also be involved. A paper not mentioned by the authors, in which such an involvement is described, is van Hoof (2002). Van Hoof provides a model of the pathogenesis of schizophrenia, in which the drive and guidance mechanisms in the brain (specific brain regions are mentioned) are said to be underdeveloped (in the terminology of the target article, they do not *coordinate* well). Such intentional aspects fit well with the model of P&S.

The target article ends by stating many open questions. Yet, one puzzle that has been ignored is the claim in Menninger et al. (1963) that some of the schizophrenic patients get "weller than well."

The theory of mobile systems (also see Milner 1999) goes beyond that of communicating ones. The intended model in ICT (Information and Communication Technology) is that of mobile telephones, or Web pages with links. Here, the number of action channels is variable and a communication may create a new channel between other processes. This theory may model very well the way in which cells communicate. In some cases, there is no receptor in a cell for a certain transmitter *T,* but there is for another transmitter *T′*. Reception of *T′* will cause the DNA code for the receptor for *T* to be read from the genome, and brought to expression, so that *T* can be received.

NOTES

1. A typical example of a communicating process is a vending machine. It has a slot for coins and one button for coffee and one for tea. The process of the machine is:

$$M = \text{want\_coin}.(\text{ready\_tea-button} + \text{ready\_coffee-button}).M.$$

This means that the machine (M) is waiting for a coin and, after that, for a push on either the tea or the coffee button. Here, the period (.) stands for sequential composition and the (+) for choice. The M is repeated on the right-hand side because we'd like the machine to keep operating. A human that regularly wants to use the machine has the process:

$$H = \text{put\_coin}.(\text{push\_tea-button} + \text{push\_coffee-button}).H.$$

Now, the interaction of the human (H) with the machine (M) is denoted by H‖M. Provided that we postulate that there are communications *c,* such that:

$$\begin{aligned} c(\text{put\_coin},\text{want\_coin}) &= \text{accept\_coin} \\ c(\text{push\_tea-button},\text{ready\_tea-button}) &= \text{pour\_tea} \\ c(\text{push\_coffee-button},\text{ready\_coffee-button}) &= \text{pour\_coffee} \end{aligned}$$

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and that noncommunicating processes (like *c[push_coffee-button,ready_tea-button]* are abstracted away, we obtain:

$$H \| M = \text{accept\_coin}.(\text{pour\_tea} + \text{pour\_coffee}).(H \| M)$$

This is indeed the outlook on the world from the point of view of such a vending machine (we left out considerations that the machines need to be refilled, and that water and energy are available in unlimited quantities). We see the difference with ordinary algorithmic programming, which is directed towards termination. Programming a process is often directed in an interactive environment to unlimited continuation.

The theory of communicating systems carefully describes processes with a global control, versus ones with a local distributed control without global knowledge.

Context rules

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Abstract: It is proposed that cortical activity is normally coordinated across synaptically connected areas and that this coordination supports cognitive coherence relations. This view is consistent with the NMDA-hypoactivity hypothesis of the target article in regarding disorganization symptoms in schizophrenia as arising from disruption of normal interareal coordination. This disruption may produce abnormal contextual effects in the cortex that lead to anomalous cognitive coherence relations.

The human brain is an engineering marvel. Its range of capabilities far surpasses that of any animal or machine. Understanding the factors that give the human brain its unique cognitive abilities is of central importance to numerous human endeavors. Awareness has been growing in recent years that a major factor determining the brain's computational power is its connectional complexity (Stone & Kotter 2002). While it is commonly agreed that cortical areas are specialized for processing different types of information, relatively little attention has been given to the dependence of this specialization on the connectional architecture of the cortex. A major determinant for an area's ability to process a certain type of information is the inputs that it receives. Yet, the connections between areas appear to be overwhelmingly supported by bidirectional pathways, implying that, through recursive interactions, an area's inputs from other areas will be affected by the output signals that it sends to them. Therefore, it would seem that the unique processing that is characteristic of each cortical area must be defined in terms of its interactions with other areas. It is therefore necessary, in seeking to determine the function of a cortical area, to consider the collection of areas with which it is connected, and with which it may jointly process information. This collection has been called an area's "connection set" (Bressler 2002) or "connectional fingerprint" (Passingham et al. 2002).

The anatomical pathways linking the areas of a connection set are undoubtedly crucial for defining what inter-areal interactions are possible, but the specific interactions that occur will ultimately depend on the dynamics of inter-areal coordination (Bressler & Kelso 2001). Phillips & Silverstein (P&S) are amply justified in addressing the basic question of how specialized cortical processes are coordinated (Varela et al. 2001). They rightly stress the importance of dynamic coordination in visual perception (Bressler 1996) and its possible disruption as a determinant of schizophrenia (Bressler 2003). Moreover, they correctly assess the importance of coordination for the issue of local contextual effects within cortical areas (Bressler 1999; 2002).

P&S are on weaker ground, however, when they attempt to formulate a general principle of cortical function from the distinction between primary and contextual influences. To define the "primary input" to cortical neurons as arising from their receptive fields, as P&S do, is a decision fraught with difficulties. The concept of receptive field cannot serve as a sound basis for deriving a universal computational property of cortical neurons. Neurons in non-sensory cortical areas do not have unambiguous receptive fields, and neurons in higher-level sensory areas have large receptive fields that derive from multiple converging inputs rather than clearly defined primary inputs. In short, cortical areas with a clearly defined primary input pathway are the exception rather than the rule.

The overall lack of primary inputs should not, however, be taken to denigrate the role of local context in cortical processing. In a broad sense, all inputs to a cortical area may be considered as contextual – even those primary inputs that can obviously be defined as directly originating in the periphery. Therefore, contextual influence may be seen as a common outcome of cortical function, a property that emerges from the coordinating interactions in which a cortical area engages with the other areas of its connection set. Included within the various types of coordinating interactions may be top-down effects from high-level areas (connectionally far from the periphery), as well as bottom-up effects from low-level areas (connectionally near the periphery).

From this perspective, the interactions that a cortical area undergoes in conjunction with the members of its connection set, automatically provide context for that area's local processing (Bressler & Kelso 2001). An understanding of the rules that govern the contextual influences exerted by cortical areas on one another may come from the study of cognitive coherence (Thagard 2000). If we assume that cognitive domains are spatially mapped in the cortex, then the dynamic coordination of cortical areas, constrained by the cortical connectional architecture, may instantiate cognitive coherence relations. In this interpretation, cognitive state depends on interacting cortical areas, which normally reach a consensus that resolves cognitive coherence and incoherence relations among participating cognitive domains. Large-scale networks of coordinated cortical areas that emerge during cognitive processing consequently reflect the recruitment and exclusion of areas according to the satisfaction of these relations. Areas that are able to express mutually consistent information are included in these networks, thereby satisfying coherence relations (positive constraint). Conversely, areas that would express information that is inconsistent with any of the included areas are excluded from participation, thereby satisfying incoherence relations (negative constraint). This viewpoint is consistent with that of P&S when they assign a functional role to cognitive coordination in schemata conflict resolution.

A prediction from this perspective is that cognitive dysfunction of the type presented by the disorganization syndrome in schizophrenia reflects an underlying discoordination of cortical areas (Bressler 2003). This interpretation is consistent with the NMDA-hypoactivity hypothesis proposed by P&S if one assumes, as they do, that inter-areal constraints are mediated by NMDA synapses. In neural terms, inter-areal discoordination would mean that cortical areas were unable to maintain a proper balance between engagement in and disengagement from large-scale coordinated networks (Bressler & Kelso 2001). In terms of cognitive coherence, discoordination would be expected to result in cognitive states marked by a breakdown of coherent relations and the manifestation of incoherent ones. The disruption of coordination between areas that normally would be coordinated might appear phenomenologically as a failure to make correct associations among sensory fragments, percepts, events, or concepts, depending on the areas involved. The coordination of areas expressing inconsistent information could result in erroneous associations among those same entities. Therefore, discoordination could produce both degradative and illusory symptoms in schizophrenia. These predicted effects would not involve a malfunction of the activity within any cortical area, so they could not be detected by recording the activity of any single neuron or single area. Rather, they would have to be detected as departures from normal patterns of coordination, reflecting violations of the normal rules of context.