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Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia

William A. Phillips
Department of Psychology, Center for Cognitive and Computational Neuroscience, University of Stirling, Stirling FK9 4LA, Scotland, United Kingdom.
wap1@stir.ac.uk

Steven M. Silverstein
Department of Psychiatry, Psychotic Disorders Division, Weill Medical College of Cornell University, New York Presbyterian Hospital, White Plains, NY 10605
steven.silverstein@att.net

Abstract: The concept of locally specialized functions dominates research on higher brain function and its disorders. Locally specialized functions must be complemented by processes that coordinate those functions, however, and impairment of coordinating processes may be central to some psychotic conditions. Evidence for processes that coordinate activity is provided by neurobiological and psychological studies of contextual disambiguation and dynamic grouping. Mechanisms by which this important class of cognitive functions could be achieved include those long-range connections within and between cortical regions that activate synaptic channels via NMDA-receptors, and which control gain through their voltage-dependent mode of operation. An impairment of these mechanisms is central to PCP-psychosis, and the cognitive capabilities that they could provide are impaired in some forms of schizophrenia. We conclude that impaired cognitive coordination due to reduced ion flow through NMDA-channels is involved in schizophrenia, and we suggest that it may also be involved in other disorders. This perspective suggests several ways in which further research could enhance our understanding of cognitive coordination, its neural basis, and its relevance to psychopathology.

Keywords: attention; cerebral cortex; cognitive coordination; cognitive neuropsychiatry; cognitive neuropsychology; context disorganization; Gamma rhythms; Gestalt theory; glutamate; grouping; memory; NMDA-receptors; PCP-psychosis; perceptual organization; schizophrenia

1. Introduction

Cognitive neuroscience provides a new conceptual framework for psychiatry by showing how psychological processes arise from neuronal activity (Kandel 1998). Conversely, it is possible that psychiatry will influence the future development of cognitive neuroscience by encouraging a better balance between localist and holistic conceptions of brain function. An apparent conflict between these conceptions has been central to the development of neuroscience, with the emphasis upon locally specialized functions emerging as clearly dominant. Neuroanatomy, neurophysiology, neuropsychology, and neuroimaging all show that different regions of the brain process information about different things, and that different cells within regions deal with different aspects of those things. Recent developments in experimental and theoretical neurobiology, however, are leading to an increased emphasis upon interactions that coordinate the activity of locally specialized processors. Here we argue that impairment of these coor-

William A. Phillips, Ph.D., is Professor of Neuropsychology at the University of Stirling, Scotland UK. He has published more than 70 papers on vision, visual memory, perceptual learning, childrens drawings, the effects of brain damage on reading and writing, and the theory of neuronal computation. He was a founder and the first Director of the Center for Cognitive and Computational Neuroscience at the University of Stirling.

Steven M. Silverstein, Ph.D., is Associate Professor of Psychology in Psychiatry at the Weill Medical College of Cornell University, in White Plains, NY, USA. He has published approximately 50 papers in the areas of schizophrenia and cognition. These include studies of information processing deficits in schizophrenia and other neurologic and developmental disorders, as well as demonstrations of treatment approaches to rehabilitate these impairments.

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dinating interactions may be central to some psychiatric disorders. Studies of such disorders may therefore shed further light on their nature and importance.

Many studies indicate that the strength and salience of neuronal responses depends on context, and that subsets of neuronal responses are grouped by synchronizing the spiking activity of which they are composed (Gray 1999; Phillips & Singer 1997a). This implies that context can change the salience and timing of neuronal signals but without changing what they mean. These effects are a special kind of modulation, which we will refer to as cognitive coordination. Such effects were predicted by theoretical considerations (e.g., Edelman 1989; Sporns et al. 1989; von der Malsburg & Schneider 1986), and Phillips and Singer (1997a) combine the experimental evidence with neurocomputational theory to argue that it is fundamental to normal cortical function. Many others agree with this view (Phillips & Singer 1997b), and the possibility that contextual coordination may be impaired in schizophrenia was briefly noted by Silverstein and Schenkel (1997). This paper examines that possibility in detail. The viewpoint presented is consistent with the theory relating schizophrenia to re-entrant mechanisms (Edelman 1989; Tononi & Edelman 2000), and with the disconnection hypothesis (Dolan et al. 1999; Friston 1999), with which it will be compared in section 7.1.

Changes in the effects of context are central to several influential theories of cognition in schizophrenia (e.g., Cohen et al. 1999a; Cohen & Servan-Schreiber 1992; Gray et al. 1991; Hemsley et al. 1993; Shakow 1962). They are not central to a currently influential conception of the underlying pathophysiology (e.g., Olney et al. 1999), however. This hypothesizes that under-activity of NMDA (N-methyl-D-aspartate) glutamate receptor channels plays a central role, and it is supported by a rapidly growing body of neuropharmacological studies cited below. Here we argue that these two streams of research are mutually supportive.

Many patients diagnosed with schizophrenia have impairments in perception, pre-attentive sensory gating, selective attention, working memory, and long-term memory, as well as other cognitive impairments more obviously interpreted in terms of context. We will argue that all these impairments involve cognitive coordination. As our theory predicts, they are most prominent in patients with thought disorder and other disorganized symptoms, so those are the symptoms on which we focus. Liddle (1987) reported evidence for three distinct groups of symptoms in schizophrenia: reality distortion (hallucinations and delusions), negative symptoms, and cognitive disorganization. Though subsequent factor analytic studies sometimes also suggest one or two additional factors, they reliably find evidence for these three (Andreasen et al. 1995). To a crude first approximation they can be seen as relating to Kraepelin's classic distinctions between paranoia, catatonia or negativism, and hebrephrenia, with the crucial proviso that they provide a 3-dimensional space that can be used to characterize some of the variation in schizophrenic symptomatology, without at all implying that patients are clustered within one of three separate regions of that space.

After 100 years of research on schizophrenia, it is still unclear whether schizophrenia is one disorder or several. The presenting symptoms are clearly heterogeneous, and at the neurobiological level multiple neurotransmitters and brain regions have been implicated (e.g., Benes 2000b; Jentsch & Roth 1999). Recognizing this heterogeneity, we must make clear at the outset that we are here primarily concerned with the disorganization syndrome, and with the disorders of coordinating neuronal interactions, such as under-activity of NMDA-receptor channels, from which disorganization may arise.

It is sometimes suggested that much of the observed heterogeneity arises in various ways from a common underlying pathology. We will argue that the disorganization syndrome, which has a particularly large genetic loading (Cardno et al. 2001), may reflect such a pathology.

Nevertheless, we do not claim that this can explain all symptoms that have been associated with schizophrenia, and assume that some can arise independently of either cognitive disorganization or NMDA-hypofunction. Similarly, we do not attempt to explain all of the many neuropathological findings relating to schizophrenia, but focus on those that seem particularly relevant to our hypothesis.

We will discuss four crucial issues concerning cognitive impairments. First, what is "context"? Second, do changes in context-sensitivity underlie various apparently diverse cognitive impairments? Third, how are cognitive impairments related to clinical symptoms? Fourth, are these cognitive changes similar to those produced by substances such as PCP (phencyclidine) and ketamine, and, if so, what does that suggest about the pathophysiology of the underlying cognitive changes?

Dopamine dysregulation has been implicated in schizophrenia by a vast amount of research, but we will outline evidence suggesting that there is also a central role for underactivity of NMDA glutamate receptor channels. For brevity we will refer to this as NMDA-hypoactivity.

We will discuss three issues raised by this evidence. First, why does NMDA-hypoactivity have such widespread but distinctive effects upon cognition? Second, what is the role of NMDA-mediated interactions between pyramidal cells in producing these effects? Third, the most distinctive property of NMDA-channels is that, in addition to being ionotropic, they are voltage-dependent. Theories of cortical computation claiming that NMDA-channels play a major role in coordinating activity (e.g. Phillips & Singer 1997a; Sporns et al. 1989) emphasize this property, and thus predict that NMDA-hypoactivity will impair cognitive coordination.

We will cite previous work clarifying the key notions of "context" and "coordination" from psychological, neurobiological, and computational perspectives, but we see these concepts as open to further improvement. We will focus on coordination within the cortex but assume that it is also relevant to limbic, striatal, and thalamic functions. Although context has long been thought relevant to schizophrenia (e.g. Shakow 1962), different investigators think of it in different ways (Pickering 1993). Cohen and Servan-Schreiber (1992) identify context with task-relevant information supplied by preceding events and stored in a working memory (WM) involving the prefrontal cortex (PFC). For others (e.g., Gray et al. 1991; Hemsley et al. 1993; Jones et al. 1991) it includes effects of concurrent context on perception, and depends more upon long-term memory than upon working memory (WM). Our concept of context includes both of these views. It is based upon an underlying distinction between processes that determine what neural signals mean, that is, what they transmit information about, and processes that affect transmission of those signals without becoming part of their meaning. Effects upon salience or timing provide good examples because it is assumed that

they do not change the meaning of the signals affected. We will call the input about which a processor transmits information to subsequent processors the "primary input." It arises from the receptive field (RF) input determining the stimuli to which cells are selectively sensitive. Context arising from other streams of processing plays a secondary role by modifying signal detection decisions, by influencing the choice between possible interpretations, by making relevant signals more salient, and by grouping those that go together. The input producing these effects has therefore been called the contextual field input (Phillips & Singer 1997a). We do not identify context with particular kinds of knowledge, but with a particular class of effects, assuming that the outputs of most processors serve both as a basis for computing higher-order things and as a context for the processing of other things. Although we discuss the distinction between contextual interactions and the primary interactions that determine RF selectivity as though it were categorical, the biological reality may well be less simple, combining these two functions in various ways.[1] Even if this is so, however, it remains necessary to make the concept of contextual interaction clear. Formal computational studies of our conception of context will be cited below. Here we try to convey the essentials through informal demonstrations.

Information can be ambiguous in several ways as the presence, interpretation, and relevance of signals can all be uncertain given just those signals alone. Figure 1 shows examples of disambiguation by concurrent stimulus context, making explicit the properties that distinguish the effects of context from the effects of primary input. Figure 1 emphasizes the effects of concurrent stimulus context, and deficits in such effects will be emphasized below. Task contexts are also important, however. Many paradigms have been used to study the effects of task-context in schizophrenia, and these effects are also usually much reduced (e.g., Perlstein et al. 1998).

Local stimulus elements are related to the context in which they occur by being grouped into coherent wholes or Gestalts. Evidence reviewed in section 4.1 shows that these basic organizational processes are often impaired in schizophrenia. The Gestalt theory-influenced psychiatrists Matussek (1952/1987) and Conrad (1958) saw core components of schizophrenia as arising from a disorder of perceptual organization, and Cutting (1989) concluded that Gestalt theory offers an understanding of otherwise inexplicable phenomena of schizophrenia. Here, we further develop these hypotheses by reviewing evidence that, as the Gestalt psychologists emphasized, such dynamic organizational processes may apply to cognition in general.

In summary, our working conceptions of coordination and context are as follows. Coordinating interactions are those that affect the salience or dynamic grouping of neuronal signals without changing what they mean. Such interactions do affect the interpretation of stimulus inputs, however. This is shown in Figure 1 where the interpretation of stimulus items is strongly influenced by surrounding items. We assume that this involves increasing the salience of the neuronal signals that convey the interpretation selected, which implies that those signals can be made more salient, without changing what they mean. Dynamic grouping creates new combinations of items while maintaining their distinct meanings. It is essentially the same as "compositionality" (Fodor & Pylyshyn 1988), which refers to the ability to compose new structures, such as sentences, from elements,

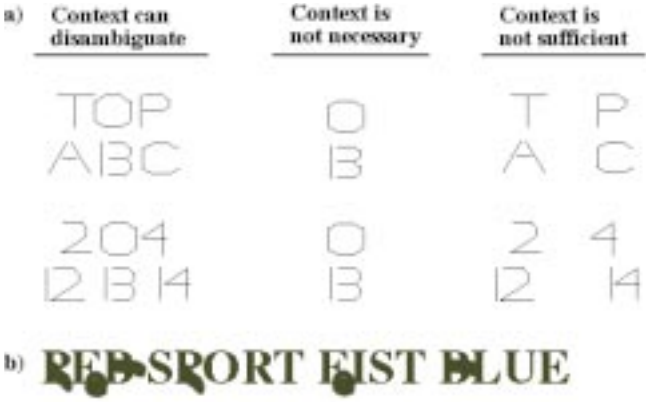

Figure 1. Simple examples showing the distinct roles of primary and contextual input, in the case of disambiguation by concurrent stimulus context. (a) *Left column:* nearby items affect the salience of the various possible interpretations of the central item. Though T and P influence the processing of O, a response identifying it as a letter rather than a digit does not imply that it is flanked by T and P, or indeed by any context at all. Thus the response transmits information about the primary input, and not about the context, even though it is affected by the context. *Center column:* context is not necessary as the central item is perceived in the absence of any context, though interpretation may then either select a dominant default option or fluctuate between alternatives. *Right column:* Primary input is necessary, however, as contextual items alone do not produce perception of items for which there is no primary evidence. (b) Mutual contextual disambiguation can occur when all items are ambiguous.

such as words, which retain their individual meanings while being used in many different combinations. Fodor and Pylyshyn (1988) argued that standard connectionist models fail to provide this capability and are therefore of limited value in modelling higher aspects of cognition. The coordinating interactions emphasized here could overcome this limitation because forming new combinations of elements while retaining their individual meanings is one of their central functions.

It may seem that localist conceptions of brain function have long since won the debate with holistic conceptions by explaining coordination in terms of a central executive located in specialized regions of the pre-frontal cortex (PFC). This cannot be the whole story, however. Organizing activity by imposing top-down strategic commands upon what would otherwise be anarchy could not by itself be adequate, because any strategic control system must be ignorant of nearly all of the details upon which effective local cooperation depends. In relation to perception it is now clear that the dynamic organizational processes emphasized by Gestalt psychology are largely pre-attentive (Watt & Phillips 2000). In relation to motor control, the long-established principle of "central executive ignorance" implies that dynamic coordination is largely local (Kelso 1995; Turvey 1977). Our working hypothesis is therefore that cortical activity is coordinated by widely distributed local interactions within and between regions, as well as by top-down strategic commands, and we will outline evidence that this is so.

These arguments imply that there are higher-level processes of strategic coordination.[2] Our working hypothesis is that local and strategic coordination both depend on basic

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physiological mechanisms of dynamic grouping and contextual-modulation. In the following section we discuss the relevance of these mechanisms to pre-attentive perception. Here we briefly note their possible relevance to executive functions. The control of lower-level routines clearly requires modulatory interactions, as does attention. Working memory requires forming and maintaining a novel sub-set of items, which implies some form of dynamic grouping (Lisman et al. 1998; Luck & Vogel 1997; Raffone & Wolters 2001). Source memory and the assignment of affective significance both imply that contextual associations are formed from semantically distinct items, thus requiring compositionality. Lastly, although it is not known what neuronal processes are involved in creative problem-solving, they seem likely to include both dynamic organization and context-sensitivity.

What we call local coordination has much in common with "contention scheduling" (Shallice 1988; Shallice & Burgess 1996), that is, with the automated resolution of conflicts between schemata. Our emphasis upon local coordination does not imply that we think executive functions have little to do. On the contrary, there is evidence that, in addition to their other roles, executive functions can modulate local processes of dynamic coordination (Fries et al. 2001; Gilbert et al. 2000; Ito & Gilbert 1999).[3]

Our perspective on context and coordination has been presented here informally, but it has been given rigorous mathematical specification using Shannon's information theory (Phillips et al. 1995; Tononi et al. 1994; 1996), and it has been implemented in simulations of simplifying (Kay et al. 1998) and physiologically realistic (Sporns et al. 1989) neural networks. Introductory nonmathematical reviews of this work that discuss its relevance to cognition are available (Phillips & Singer 1997a; Tononi et al. 1998b). Computational theories provide ways of bridging the gap between psychiatry and neurobiology (e.g., Cohen & Servan-Schreiber 1992; Hoffman & McGlashan 1993). An explicit bridge is necessary, because we will never know whether an identified neural pathology is directly responsible for the cognitive impairments with which it is found to be associated unless we know how the mechanism that is impaired gives rise to the cognitive capacities concerned.

The central concern of this target article is therefore with the neural bases of cognitive disorganization in schizophrenia. Section 3 reviews evidence implicating NMDA-hypofunction in this disorder. Section 4 reviews evidence that it involves deficits in basic processes of cognitive coordination, such as contextual disambiguation and dynamic Gestalt organization. We claim that the neurocomputational theories of Kay et al. (1998), Phillips et al. (1995), and Tononi et al. (1994) can explain why NMDA-hypofunction should lead to these particular cognitive deficits. Section 2, therefore, first reviews psychophysical, anatomical, and physiological evidence for the central ideas expressed in those theories. The computational work simply shows that the operations involved are formally coherent and able to perform the functions involved. Empirical studies are necessary to determine whether they are relevant to neurobiology. Section 5 reviews studies of high-frequency cortical rhythms that provide further support for the view that cognitive coordination, NMDA-activity, and psychosis are all related. Section 6 shows how our perspective is compatible with the heterogeneity of symptoms in schizophrenia, and also briefly discusses the possibility that impaired cognitive coordination may be involved in some other disorders of mental function, such as autism. Section 7 compares our perspective with related theories. Section 8 lists several of the issues that arise, and which in our opinion deserve closer examination.

2. A special class of neuronal interactions coordinate cortical activity

2.1. There is physiological and psychophysical evidence for coordinating interactions

There is good evidence that both stimulus and task contexts affect activity by enhancing relevant and suppressing irrelevant activity. For example, parallel studies comparing results obtained from human psychophysics and single-unit recording in the visual cortex of alert monkeys show that they are quantitatively very similar (Kapadia et al. 1995). Here we outline this evidence, which has been thoroughly reviewed by others (Desimone & Duncan 1995; Gilbert 1992; Kovács 1996; Lamme & Spekreijse 2000; Maunsell 1995; Salin & Bullier 1995; Singer & Gray 1995; Wörgötter & Eysel 2000; Zipser et al. 1996). Context influences the salience of neuronal responses. Pyramidal cells in the primary visual cortex, for example, are specialized to respond preferentially to stimuli with particular positions, orientation and size. This selectivity is determined by the primary input to each cell, which arises from a limited region of the visual field which is called the receptive field (RF) of that cell. Responses to preferred stimuli within the RF can be amplified or suppressed by stimuli presented well beyond the classical RF, however. This interaction is highly specific to the geometric relations between elements, with facilitation being strong when the local elements taken together form some coherent entity such as a smooth contour (Kapadia et al. 1995; Kovács 1996). Facilitation is strongest when the RF input is weak, and decreases as the spacing between elements increases (Polat et al. 1993; Polat & Sagi 1998). Locally specific contextual amplification in primary visual cortex has also been shown to be produced by feedback signals from extrastriate cortex that increases the salience of stimulus elements that are part of the figure rather than the ground (Zipser et al. 1996). Though in a sense "top-down," these particular effects are nevertheless still driven by stimulus context, which is used automatically to organize input into figure and ground (Zipser et al. 1996). Similar effects on salience can also be produced by processes of selective attention that depend upon the task (Desimone & Duncan 1995; Maunsell 1995). These effects of task context are produced by the same kind of physiological mechanisms as those that mediate the effects of stimulus context (Treue & Tujillo 1999). Furthermore, task context modulates the effects of local stimulus context (Gilbert et al. 2000; Ito & Gilbert 1999).

Contextual interactions are also involved in the grouping of neuronal responses. The conditions in which simple visual elements, such as Gabor patches, are grouped, are so similar to those under which disambiguating interactions occur between them, that both effects could depend upon a common set of underlying neuronal connections (Kovács 1996). Dynamic Gestalt grouping has a fundamental role in vision, and is predominantly computed by pre-attentive mechanisms. One particularly clear example of a task in which dynamic grouping is necessary is the computation of

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coherent object motion from many local motion signals (Watt & Phillips 2000), and relevant studies of motion perception in schizophrenia will be discussed in section 4.1.

Dynamic grouping could be signalled by synchronizing the activity to be grouped, and this hypothesis is supported by a wide variety of evidence (Gray 1999; Singer 1994; 1995; 1999; Singer & Gray 1995). Synchrony was first observed in primary visual cortex of anaesthetised cats, and it has since been shown in awake monkeys (Kreiter & Singer 1996), and within and between parietal and motor cortex (Roelfsema et al. 1997). Psychophysical evidence on the role of dynamic grouping in vision and its relation to synchrony is reviewed by Watt and Phillips (2000). Evidence from evoked potentials indicates that synchrony is enhanced by selective attention in auditory cortex (Tiitinen et al. 1993), and it has been argued that synchrony may be the neural correlate of sensory awareness (Engel & Singer 2001). Though the role of synchrony remains controversial, Treisman (1999) concludes that there is so much evidence for grouping through convergence in pre-specified hierarchies and for grouping as signalled by synchronization that it is highly likely that both occur. Watt and Phillips (2000) argue that they are mutually supportive.

2.2. Lateral and descending intracortical connections provide an anatomical basis for coordination

Long-range communication within and between cortical regions is mediated predominantly by pyramidal cell axons (Braitenberg & Schüz 1991). Though complex, this long-range communication includes some simple patterns of connectivity that are common to cortex as a whole (Felleman & Van Essen 1991). Ascending feedforward connections provide the primary driving inputs that are processed by local cortical circuits. Long-range lateral connections within and between regions together with descending feedback connections provide additional input (Felleman & Van Essen 1991), and this could in part be used to coordinate the primary feedforward processing. This general pattern of connectivity is shown as simply as possible in Figure 2a. Figure 2b uses the canonical circuit hypothesized by Douglas and Martin (1990) to show how local circuits within cortical columns could receive both primary ascending inputs and long-range coordinating inputs. Figure 2 focuses on long-range connections omitting many details of intrinsic connectivity within the local circuits, such as the NMDA-receptor component of the local excitatory input to the inhibitory cells (Grunze et al. 1996). The long-range lateral connections within primary visual cortex have been studied in great detail. They are highly specific, and probably implement the coordinating interactions producing Gestalt organization (Gilbert 1992; Kovács 1996; Schmidt et al. 1997; Singer & Gray 1995).

2.3. NMDA glutamate receptor channels provide a synaptic mechanism for coordination

The cholinergic, adrenergic, dopaminergic, and serotonergic systems are most prominent amongst neurotransmitters known to have modulatory effects. It is unlikely that these classical neuromodulators can implement the detailed coordinating interactions emphasized here, however. This is because those interactions must be between the processing streams that convey detailed information about what is be-

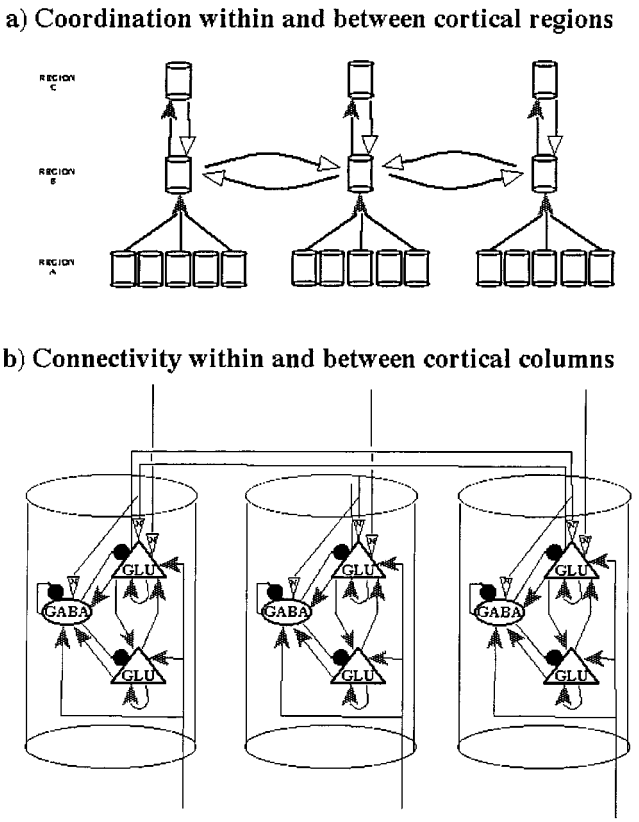

Figure 2. Common patterns of connectivity within and between cortical regions. (a) This shows the hypothesized distinction between RF connections that transmit primary feedforward information through cortical columns, shown with solid grey arrowheads and contextual field connections that coordinate that transmission, shown with open arrowheads. Only a few columns are shown in each region, and many complexities of connectivity are omitted. Each column of necessity receives input from only a small subset of the cells in the preceding region, and though these subsets may overlap for nearby columns (not shown) there is little overlap between the inputs of most columns within a region. Massively parallel but interactive processing is thus implied by this architecture. (b) Connectivity within and between columns is shown using the canonical cortical circuit hypothesized by Douglas and Martin (1990). Three columns processing separate parts of the input from the preceding region are shown. This pattern of connectivity is thought to occur throughout the cortex. Glutamatergic (GLU) pyramidal cells are divided into two populations with the upper group being those in Layers II, III, and IV and the lower being those in Layers V and VI. Excitatory synapses are shown by arrowheads. Inhibitory synapses formed by inhibitory cells are shown by filled circles. Synapses mediating long-range coordination within and between regions are shown by open arrowheads labelled N. They selectively link columns sensitive to distinct but correlated inputs, bypassing intervening columns that respond to inputs that are less correlated. The circuitry shown is highly simplified and omits much detail, including the pyramidal cell outputs to more distant sites, and the sources of the descending coordinating inputs from higher regions. For detailed reviews of evidence on which this figure is based, see Douglas and Martin (1990), Felleman and Van Essen (1991), and Salin and Bullier (1995).

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ing seen, heard, thought, or remembered, and so on. Consider the perception of the ambiguous stimuli in Figure 1, for example. Coherent interpretations at each level of processing are formed by coordinating the interpretation of each element with that of other elements. The information concerning these elements and their interpretation is transmitted by the axons of pyramidal cells, which are all glutamatergic (Braitenberg & Schüz 1991). We therefore suggest that two major components of the glutamatergic system need to be distinguished: The first provides the primary input that produces post-synaptic output and determines what cells transmit information about. The second is neither necessary nor sufficient to produce post-synaptic output, but modifies the effects of the primary inputs. These modulatory interactions between pyramidal cells can be direct, but will often be mediated by local circuit neurons, as in the case of suppressive interactions for example, which depend on inhibitory interneurons. This distinction between primary and coordinating interactions is closely analogous to that between obligatory and modulatory interactions between cortical regions as inferred from fMRI (functional magnetic resonance imaging) data (Friston et al. 1995).

This argument is supported by a well-established distinction between two classes of glutamate receptor, one that produces primary excitatory drive and one that modulates the activity thereby produced. For a thorough introduction to these receptors see Feldman et al. (1997). AMPA and kainate glutamate receptors provide primary excitatory drive because they open whenever glutamate (GLU) binds to them. Metabotropic and NMDA-receptors both have a coordinating role, because both modulate the effects of direct excitatory inputs (Daw et al. 1993; Salt & Eaton 1996). Though there may be a role for metabotropic receptors (Whittington et al. 1995), coordination on a fast time-scale is likely to be more dependent on NMDA-receptors because they operate more rapidly (Daw et al. 1993). This argument is made precise by computational studies showing how the voltage-dependent properties of NMDA-receptors can be used for the dynamic organization of both processing and learning (e.g., Kay et al. 1998; Phillips et al. 1995; Sporns et al. 1989). The argument is further strengthened by the evidence cited below, implicating NMDA-receptors in cognitive coordination.

As NMDA-receptors may play a crucial role in coordination we now note their most relevant characteristics: (1) They are voltage-dependent because at or below resting levels of post-synaptic membrane potential, they are blocked by magnesium ions (Fig. 3). Current flow through NMDA-channels thus requires both that glutamate binds to the receptor and that the post-synaptic membrane is already partially depolarized. The key point to note is that because of this voltage-dependency they could contribute to coordination by amplifying activity that is appropriate, and by suppressing, via inhibitory interneurons (Grunze et al. 1996), that which is inappropriate. They therefore have a gain-control effect on ongoing processing, as shown in Figure 3c (based on data in Fox et al. 1990). (2) They let calcium into the cell, and thus play a major role in the cascade of processes that underlie learning. (3) They open less rapidly than non-NMDA-channels, and open for longer. Note, however, that direct application of NMDA to neural circuits can activate rhythmic bursting (Daw et al. 1993), and that NMDA currents may have a rapidly decaying component with a time constant short enough to support fast bursting and synchronization (Jensen et al. 1996). (4) They have a rich set of sites that regulate channel function. Figure 3 shows only a few of them. (5) They are widely distributed across all cortical regions, and are especially dense in the hippocampus, basal ganglia, and pre-frontal cortex (Monaghan et al. 1989). (6) At the cellular level they form synapses on both pyramidal cells and on inhibitory interneurons (Grunze et al. 1996), and in the case of pyramidal cells they are predominantly located on distal dendrites (Siegel et al. 1994), which supports the hypothesis that it is predominantly the distal dendrites of pyramidal cells that receive long-range contextual input (Körding & König 2000). (7) They have several subtypes, with subtly different physiological properties (McBain & Mayer 1994). NMDA-receptors on pyramidal projection cells and on local circuit interneurons could therefore be of different subtypes (Grunze et al. 1996; Monyer et al. 1994).

Clearly, our hypothesis concerning the role of NMDA-receptors in cognitive coordination requires further development and test. Additional support discussed in section 5.2 concerns their relevance to the high-frequency synchronous rhythms that have been related to both cognitive coordination and schizophrenia.

2.4. Coordinating interactions have general relevance for cognition

Studies of vision are prominent in the evidence cited above because they relate neurophysiology and psychophysics in great detail. Higher cognitive functions are likely to be even more dependent on context-sensitivity and dynamic grouping, however. An empirical argument for supposing that such coordinating interactions have general relevance for cognition is that the mechanisms by which they could be implemented (such as those shown in Figs. 2 and 3) are widely distributed throughout the cortex. Furthermore, as will be outlined in section 5, EEG (electroencephalogram) recordings provide evidence that high-frequency synchronization plays an important role in various cognitive functions.

3. NMDA-antagonists impair cognitive coordination and are schizomimetic

If cognitive coordination depends upon ion flow through NMDA-channels then it should be disrupted when they are blocked. The effects of subanaesthetic doses of a class of drugs that include PCP and ketamine support this prediction as they produce their psychotomimetic effects via competitive or non-competitive antagonism with NMDA-channels (Javitt & Zukin 1991). For brevity we refer to this disorder as PCP-psychosis. Many reviews of PCP-psychosis and the associated glutamatergic hypothesis of schizophrenia are available (Coyle 1996; Ellison 1995; Goff & Coyle 2001; Javitt & Zukin 1991; Jentsch & Roth 1999; Olney & Farber 1995; Olney et al. 1999; Tamminga 1998). Only particularly relevant findings are summarized here. The schizomimetic effects of NMDA-antagonists suggests that schizophrenia may involve under-activity of NMDA-receptors, so evidence on this will also be discussed. Though PCP-psychosis seems more similar to schizophrenia than any other drug-induced psychosis, they are not claimed to be identical. Abi-Saab et al. (1998) give reasons for expect-

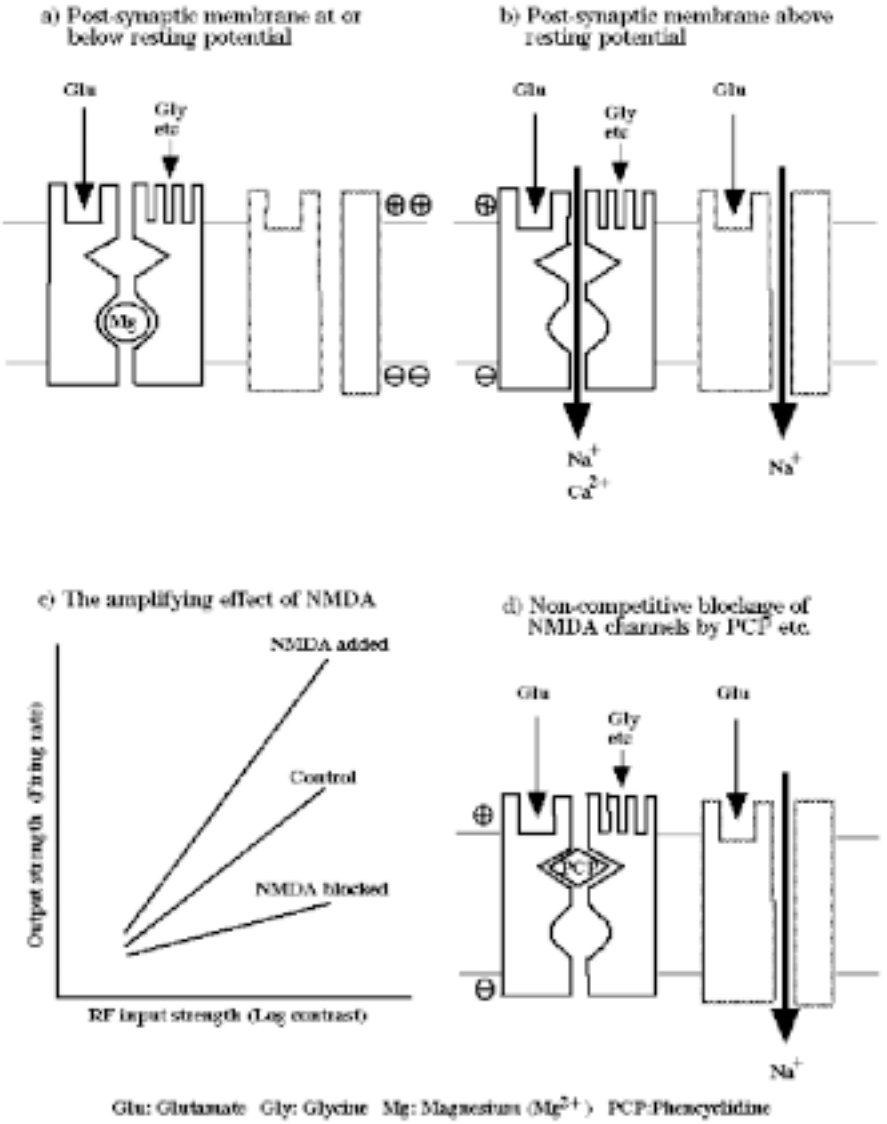

Figure 3. Outline of the voltage-dependency of NMDA receptor synaptic channels, emphasizing their amplifying function. NMDA receptor channels are shown in black outlines, non-NMDA (AMPA and KA) in grey outlines. Outward ion flow not shown. NMDA-channel function is regulated by several other sites in addition to those shown. (a) When the post-synaptic membrane is at or below resting potential, NMDA-channels are blocked by magnesium ions, which reduces ion flow through these channels when glutamate or NMDA binds to the receptor. (b) When the post-synaptic membrane is raised above resting potential, for example, by flow through non-NMDA-channels, the magnesium block is released, so ions then flow through these channels when glutamate binds to the receptor. (c) The amplifying effect of NMDA function, as shown by iontophoretic application of NMDA or of APV which blocks binding to the receptor. Graph based on the responses of cells in cat visual cortex to visual stimuli at their preferred orientation and of varying contrasts (Fox et al. 1990). (d) Binding to the PCP receptor site in NMDA-channels by phencyclidine, or its analogues ketamine, MK-801, and so on, reduces ion flow through those channels, but does not prevent flow through non-NMDA-channels.

ing differences, and conclude that the psychosis induced by NMDA-antagonists best models symptoms of cognitive disorganization including thought disorder. As we will show, it may also have relevance to other symptoms, however. Our focus here is therefore on the cognitive disorganization produced by reducing the activity of NMDA-receptor channels. NMDA-receptor antagonists, such as PCP, can influence other neurotransmitter systems also, however, so the complex psychopathology produced may also include effects due to those other influences.

Effects of NMDA-antagonists in humans are summarized in Table 1. Acute effects of a single subanaesthetic dose occur within minutes and last a few hours; chronic effects of repeated doses can be long lasting. Their similarity to effects seen in schizophrenia is both striking and surprising, given the very different developmental courses of the two conditions. The effects of acute exposure to NMDA-antagonists show that most of the symptoms and deficits seen in schizophrenia can be produced without long-term structural damage. The relevance of NMDA-antagonists to schizophrenia is further strengthened by evidence that they provoke relapse in schizophrenic patients, who are highly sensitive to them (Allen & Young 1978; Bakker & Amini 1961; Lahti et al. 1995b; Malhotra et al. 1997; Tamminga 1998). PCP-psychosis also resembles schizophrenia in that it is age dependent, with its effects being much less appar-

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Table 1. *Effects of NMDA-antagonist exposure in humans*

Effect studied	Acute Exposure	Chronic Exposure
1. *Positive Symptoms*		
Delusions	Paranoia, Reference[b]	Reference, Influence, Grandiosity, Religious[d]
Hallucinations	Visual[b] Auditory[e]	Auditory[d]
2. *Negative Symptoms*		
Negativism/Withdrawal	Emotional withdrawal, Psychomotor retardation[a,b,e]	
Affective Flattening	Yes[a,e]	
3. *Disorganized Symptoms*		
Conceptual Disorg. and/or Thought disorder	Yes[b,c,p]	Yes[d]
4. *Cognitive Deficits*		
Working Memory	Yes[i,m]	Yes[n]
Long-Term Memory	Verbal[q] Semantic[c] Declarative[m] Free Recall and Recog. Memory[h]	
Executive Functioning	WCST[b,j] Verbal Fluency[b,c] Concrete Thinking[a,e] Raven Progressive Matrices[a]	
Attention	Selective Attentiona Digit Span[a] Stroop Test[a] Increased Reaction Time[o]	Reduced Attention Span[l] Trail marking Test (B)[n]
Eye Movements	Smooth Pursuit[g]	
Context Processing	Auditory and Visual[f]	
Perception	Visual[q] Perceptual Awareness[a] Perceptual Constancy[a]	
5. *Affect*	Anxiety[b] Euphoria & Disorganization[e]	Anxiety, Euphoria, Labile[a]
6. *Brain Blood Flow*	Increase in PFC[e]	Decrease in PFC[k]

[a]Bakker & Amini (1961) [b]Krystal et al. (1994) [c]Adler et al. (1998a) [d]Allen & Young (1978) [e]Vollenweider et al. (1997b) [f]Umbricht et al. (2000) [g]Weiler et al. (2000) [h]Malhotra et al. (1996) [i]Ghonheim et al. (1985) [j]Krystal et al. (2000) [k]Hertzman et al. (1991) [l]American Psychiatric Association (1989) [m]Newcomer et al. (1998) [n]Cosgrove & Newell (1991) [o]Rosenbaum et al. (1959) [p]Adler et al. (1999) [q]Harborne et al. (1996).

ent in immature subjects (Karp et al. 1980). PET-scans (positron emission tomography) show that in healthy volunteers these drugs produce an acute increase in metabolic activity in PFC, anterior cingulate, and in parietal and sensorimotor cortex, together with decreases in hippocampus and lingual gyrus, with effects 20–40 minutes later in the thalamus and cerebellum (Breier et al. 1997; Lahti et al. 1995a; Tamminga et al. 1995; Vollenweider et al. 1997a, 1997b). Repeated administration produces a chronic decrease in PFC activity, however, so chronic PCP-psychosis may provide the best model of schizophrenia (Jentsch & Roth 1999). In vivo brain imaging, post-mortem neurochemistry, and clinical pharmacology all provide evidence of glutamatergic abnormalities in schizophrenia (Hirsch et al. 1997; Tamminga 1998). Furthermore, a recent study of post-mortem hippocampal tissue suggests that it may not be the number of NMDA-channels that is pathological, but their subunit composition (Gao et al. 2000). Further evidence for NMDA-hypofunction in schizophrenia are given in the reviews cited above. The NMDA-antagonist ketamine produces deficits very similar to those seen in schizophrenia in both the mismatch negativity paradigm, a reflection of pre-attentive contextual interactions, and in the AX version of the Continuous Performance Task, a measure of post-attentive contextual interactions (Javitt et al. 2000; Umbricht et al. 2000). The schizomimetic effects of NMDA-antagonists, including reductions in context-sensitivity, are therefore well established. We therefore need to determine how these effects occur.

Some cognitive deficits in both PCP-psychosis and schizophrenia may be due to generalized overexcitation and any consequent neuropathophysiology, rather than being direct consequences of NMDA-hypofunction. The neurotoxic effects of chronic NMDA-hypofunction are well established (Ellison 1995; Olney & Farber 1995; Olney et al. 1999). This may contribute to long-term psychopathology but is unlikely to explain the acute psychological effects of PCP, which occur within minutes and are transient. Furthermore, neuronal degeneration in schizophrenia often seems too minimal to produce the deficits observed (Tamminga 1998). The neuronal degeneration that does occur can be explained as resulting from overactivity due to the failure of NMDA-receptors to facilitate excitatory input to inhibitory interneurons (Coyle 1996; Ellison 1995; Olney & Farber 1995). Interactions with the dopamine system could also lead to overactivity. Some cognitive deficits may thus be consequences of generalized overactivity (Coyle 1996; Olney et al. 1999). It is hard to see how this can explain all of the observed deficits, however. First, it is hard to see how generalized overactivity can be used to predict the specific changes in context-sensitivity and perceptual grouping emphasized throughout this article. Increases in activity, for

example, as reflected by neuroimaging, are often assumed to be functional, not malfunctional. Second, impaired sensory gating does not reflect general overactivity because response latencies and amplitudes to individual stimuli are unaffected (Catts et al. 1995; Javitt et al. 1996). Third, neuroimaging does not show general overactivity in psychosis. Fourth, if the effects of NMDA-hypofunction were largely due to a consequent under-activity of inhibitory cells, then agonists for inhibitory cells might be prominent in pharmacotherapy, but they are not (Olney et al. 1999). Finally, many NMDA-channels are localized on pyramidal cells (Daw et al. 1993; Grunze et al. 1996; Siegel et al. 1994), and thus have facilitatory rather than inhibitory effects on pyramidal cell activity. Direct evidence that they facilitate sensory gating will be outlined below.

The role of NMDA-channels in learning is widely accepted, and learning is impaired in both PCP-psychosis and schizophrenia, so some of the other cognitive deficits may be a secondary consequence of impaired learning. This cannot account for many of the symptoms observed, however, as effects on immediate experience are prominent, which is to be expected, given the direct effect of NMDA-channels on glutamatergic activity. Furthermore, although there are some similarities between amnesia and schizophrenia, there are also clear differences (Heinrichs 1993). Impaired learning is thus more likely to be a consequence than a cause of impaired coordination.

Some of the cognitive effects of NMDA-dysfunction will arise as consequences of interactions between the NMDA-system and other neurotransmitters, such as dopamine and serotonin, and so on (Olney et al. 1999). Glutamate-dopamine interactions are complex (Coyle 1996; Jentsch & Roth 1999). Various studies suggest that reduced NMDA-receptor function can facilitate sensitization of dopamine systems (Duncan et al. 1999). NMDA-antagonists produce dopamine dysregulation (Jentsch & Roth 1999; Jentsch et al. 1997a; Moghaddam et al. 1997), for example, and these effects include an acute increase in the use of dopamine in dorsolateral PFC, followed by a chronic decrease (Jentsch et al. 1997a; 1997b; Moghaddam et al. 1997). This is compatible with theories proposing a chronic reduction in prefrontal dopamine leading to excessive mesolimbic dopamine in schizophrenia (Davis et al. 1991; Jentsch & Roth 1999). Conversely, dopamine may be involved in regulating NMDA-activity (Greengard et al. 1998; Olney et al. 1999), and there is evidence that antipsychotic drugs acting through the D2 dopamine receptor can enhance NMDA function (Goff & Coyle 2001).

Some cognitive deficits resulting from NMDA-hypofunction are therefore likely to be due to interactions with other neurotransmitter systems. Some are likely to be directly due to NMDA-hypofunction, however, as that directly alters glutamatergic transmission. The challenge before us is to sort out which is which. One way to do this is via computational theories that relate specific properties of NMDA-channels, such as their voltage-dependence, to specific cognitive functions (e.g., Kay et al. 1998; Phillips et al. 1995; Tononi et al. 1994; 1996). PCP-psychosis has from the start been interpreted in terms of processes that somehow "integrate" incoming information (Bakker & Amini 1961; Luby et al. 1962). If cognitive coordination depends on NMDA-channel activity as proposed here, then this can explain why incoherent, irrelevant, and fragmented perceptions and thoughts arise from NMDA-hypofunction.

Another way to test hypotheses concerning direct effects of NMDA-dysfunction is to test specific predictions that they make concerning cognitive changes, and substantial progress has already been made in this direction (e.g., Javitt et al. 1996; 2000; Umbricht et al. 2000). Evidence on the direct effects of NMDA-hypofunction comes from studies of the effects of NMDA-antagonists on sensory gating in auditory cortex. Impaired sensory gating occurs in both schizophrenia and PCP-psychosis (Jentsch & Roth 1999), and has been studied using mismatch negativity (Javitt et al. 1996). The response to an auditory stimulus that occurs as a deviant within a sequence of repetitive stimuli is greater than if it occurs as a repeated stimulus. This, and related effects of stimulus context, are much reduced in schizophrenia (Catts et al. 1995; Javitt et al. 1996; Judd et al. 1992), and it has been shown that NMDA-hypofunction can produce this effect (Javitt et al. 1996). NMDA-antagonists were infused into a microregion of primary auditory cortex in awake monkeys, and multichannel electrodes recorded neural activity in response to repetitive and deviant auditory stimuli. NMDA-antagonists removed the effect of stimulus context without affecting the primary obligatory response to the individual stimuli (Javitt et al. 1996). Neuronal degeneration, dopamine dysregulation, and impaired learning are all unlikely to be involved in this case, so this is evidence that reduced context-sensitivity in sensory cortex can be directly due to NMDA-hypofunction. Together with the studies of Umbricht et al. (2000), showing that ketamine impairs contextual interactions in healthy volunteers, these results therefore provide strong support for the perspective we advocate.

4. Cognitive coordination is impaired in schizophrenia

4.1. Deficits in perceptual grouping

In a study of the subjective experiences reported by patients, Cutting and Dunne (1989) found that perceptual dysfunctions were the most invariant feature of the early stage of schizophrenia. Goodarzi et al. (2000) found that, in people scoring highly on schizotypy, local processing dominates global processing, thus producing a deficit in perceptual Gestalt organization. Gestalt organization is a paradigmatic example of cognitive coordination. Many studies show that it is impaired in schizophrenia (Cox & Leventhal 1978; Knight 1984; 1992; Knight & Silverstein 1998; Place & Gilmore 1980; Rabinowicz et al. 1996; Silverstein et al. 1996a; 1996b; 1998a; 2000). These impairments are a specific feature of the illness itself. They are not due to a generalized cognitive deficit because patients perform relatively better than normal in conditions where grouping would interfere with performance (Place & Gilmore 1980; Silverstein et al. 1996a, as shown in Fig. 4). They are not an epiphenomenon of treatment, because: (1) there is no relation between either oral dose or blood level of depot medication and performance on perceptual organization tasks (Knight 1992); (2) patients medicated using traditional neuroleptics, and unmedicated patients, do not perform differently on these tasks (Rabinowicz et al. 1995); and (3) impairments have been demonstrated in unmedicated patients (Frith et al. 1983).

Perceptual grouping is far from being completely absent in schizophrenia, however. Patients perform adequately

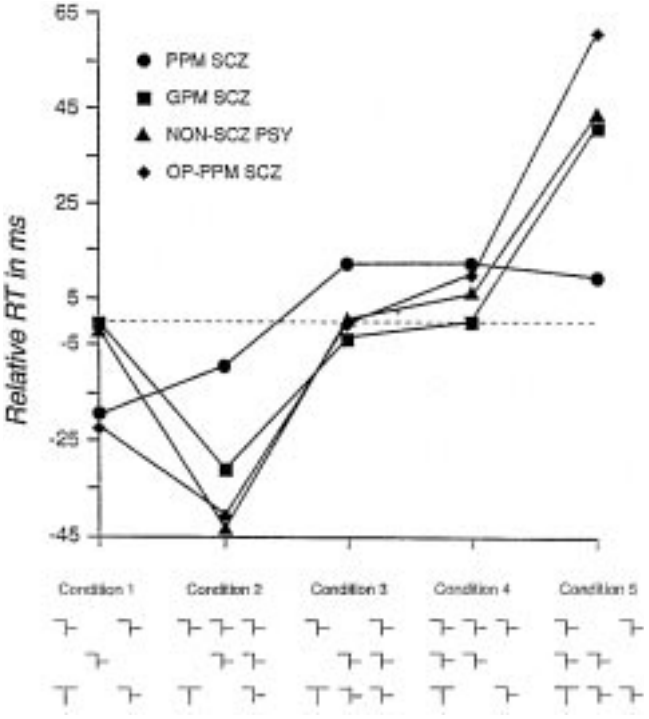

Figure 4. The effect of five different grouping conditions on mean reaction time to decide whether the letter in an array is a T or an F for four different groups of subjects. All, except for the inpatient poor premorbid schizophrenic group, show the same effects of grouping condition as that obtained with normal subjects. PPM = poor premorbid; SCZ = schizophrenia; GPM = good premorbid; PSY = psychosis; OP = outpatient (data from Silverstein et al. 1996a).

when the task involves stimuli with continuous contour or strong configural properties (Chey & Holzman 1997; Knight & Silverstein 1998; Silverstein et al. 1998d). In the absence of strong cues to grouping, however, schizophrenia patients show clear impairments in combining noncontiguous elements (e.g., dot or line patterns) into perceptual wholes (Cox & Leventhal 1978; Place & Gilmore 1980; Silverstein et al. 1996a; 1998a; 2000). Patients are also impaired in their ability to alter perceptual organization of ambiguous stimuli based on current context (Silverstein et al. 1996b), or to develop perceptual organization for unstructured patterns after repeated exposure (Place & Gilmore 1980; Silverstein et al. 1998a). Furthermore, the performance deficit shown by patients was removed by strengthening the contextual input, suggesting that they required stronger context than normal (Silverstein et al. 1996a). In addition, symmetrical stimuli comprised of noncontiguous components are not processed as groups by schizophrenia patients without strong top-down influences that use context (Knight 1992; Silverstein et al. 1998a). Schizophrenia thus involves a reduced ability to organize activity into coherent groups, but this only impairs performance when cues to grouping are weak in some way.

Perceptual grouping depends on the combined operation of two different but mutually supportive processes: grouping through convergence in pre-specified feature hierarchies; and grouping through dynamic Gestalt organization (Watt & Phillips 2000), which involves processes that create novel groupings that can be specified only after the input is known. The computation of local motion signals can be pre-specified, but the perception of the global coherent motion of a whole surface requires dynamic grouping because it depends upon working out which local motion signals arise from a single surface in each particular instance (Watt & Phillips 2000). Our perspective therefore predicts that global, but not local, motion perception will be impaired in schizophrenia. A recent psychophysical study supports this prediction (Chen et al. 2001), and fMRI data show that activity in higher motion perception areas of visual cortex is much reduced in neuroleptic-naive patients (Tost et al. 2001). These findings provide strong support for our perspective.

4.2. Deficits in contextual disambiguation

Many paradigms have been developed to study different forms of contextual disambiguation and, though diverse, all require detailed contextual information to modify the processing of information about other things. We first discuss effects that can plausibly be explained as depending on executive functions, then those that are more plausibly explained in terms of other functions. Reduced context-sensitivity in schizophrenia has been found in many paradigms designed to assess executive function and selective attention, including: the Wisconsin Card Sort Test (WCST) (Gold et al. 1997); the Stroop task (Cohen et al. 1999a; Perlstein et al. 1998); various versions of the Continuous Performance Task (CPT) (Cohen et al. 1999a; Pigache 1999); the anti-saccade task (Curtis et al. 2001); and N-back tasks (Perlstein et al. 2001). Such findings have often been replicated (e.g., Servan-Schreiber et al. 1996), and include deficits in first-episode as well as in chronic patients (Riley et al. 2000). Abnormalities in the Stroop paradigm are complex, but can be interpreted as arising from an impaired ability to focus attention on those aspects of the stimulus that are relevant to the task (Barch et al. 1999). This reduced sensitivity to task-context is most closely associated with disorganized symptoms (Barch et al 1999), that is, with the same sub-group of patients who show reduced sensitivity to stimulus-context. Contextual disambiguation is also impaired in language comprehension (Cohen et al. 1999a; Hoffman & McGlashan 1993; Kuperberg et al. 1998), and production (Barch & Berenbaum 1997; Patterson et al. 1986; Spitzer et al. 1994). These deficits have also been explained in terms of a component of WM that stores task relevant contextual information in the PFC (Cohen & Servan-Schreiber 1992).

Reduced context-sensitivity has also been found in many paradigms testing non-executive functions, including: reduced effects of irrelevant letters flanking a target letter in a choice reaction-time task (Jones et al. 1991); reduced prepulse inhibition (Adler et al. 1998b); reduced use of context for phonemic disambiguation (Rochester 1978); reduced effects of context in weight perception and related paradigms (reviewed in Magaro 1980); and reduced mismatch negativity amplitudes, which is an event-related potential that reflects preattentive perceptual processing (Catts et al. 1995; Javitt et al. 1996; 2000). Delayed-tone matching is also impaired, and is due to impaired sensory comparison of a current tone with the immediately preceding context, rather than to increased distractibility (Rabinowicz et al. 2000). The decreased amplitude of mismatch negativity

scalp potentials to unattended stimuli are found in the same patients that show deficits in the CPT (continuous performance task) (Javitt et al. 2000). The contextual interactions involved in the mismatch negativity deficit are pre-attentive, whereas those involved in the CPT deficit are post-attentive. Both deficits of contextual processing could arise from the same kind of underlying pathology, however, and this view is supported by the finding, noted in section 3, that similar deficits in both mismatch negativity and the CPT are produced in normal volunteers by ketamine (Umbricht et al. 2000).

Paradigms in which context is misleading (e.g., Jones et al. 1991; Kuperberg et al. 1998) provide strong evidence for a specific reduction in context-sensitivity, because in those paradigms context interferes with the performance of patients less than it does with that of control subjects. Reduced interference cannot be due to a general performance deficit.

Contextual disambiguation is therefore impaired in tasks that assess executive functions and in tasks that assess non-executive functions. Furthermore, as will be discussed further in section 4.4, deficits of context-sensitivity correlate most strongly with disorganized symptoms (e.g., Barch et al. 1999; Cohen et al. 1999a).

4.3. Memory deficits

Memory deficits are relevant here because, as the Gestalt psychologists emphasized, dynamic organizational processes are also important in memory functions. Both episodic and semantic memory deficits occur in schizophrenia, with the latter being relatively more impaired than in the amnesic syndrome (Chen & McKenna 1996; Duffy & O'Carroll 1994). In addition, the influence of contextual constraints between items in the recall of verbal material is reduced in thought-disordered patients (Maher et al. 1980). Long-term memory deficits are to be expected from our perspective for at least four reasons. First, NMDA-channels, synchronization, and coherence have all been implicated in long-term memory formation (Singer 1995). Second, context is important for retrieval from long-term memory. Third, it has been hypothesized that contextual interactions are important for both the learning of associations between features and the discovery of those features that are associated (Kay et al. 1998). Fourth, source memory and memory for affective significance both require the formation of assemblies that relate items to the relevant context.

Though less clear than long-term memory deficits, WM deficits have also been associated with schizophrenia (e.g., Park & Holzman 1992). Digit span is reduced from about seven to about six digits (Gruzelier et al. 1988), and short-term visual memory capacity is also reduced (Knight et al. 1985). Though such small impairments could easily be discounted, they may have important consequences for cognition under demanding or stressful conditions. WM depends upon dynamic grouping because it requires memory for novel combinations of familiar elements. Experiments with normal subjects show that only about three or four dynamic groupings can be held simultaneously in visual WM (Luck & Vogel 1997), and these groupings could be signalled through synchronization (Lisman & Idiart 1995; Luck & Vogel 1997; Raffone & Wolters 2001). Simulations of recurrent networks composed of physiologically realistic elements show rigorously how NMDA-currents can select and maintain any novel subset from a set of familiar elements (Lisman et al. 1998). Furthermore, an independent analysis of the dynamics of synaptic transmission, for example, in PFC circuits, also suggests a critical role for NMDA-receptors in WM (Wang 1999). Working memory, NMDA-currents, and dynamic grouping may therefore be closely related, and, if so, this could help explain subtle WM deficits in schizophrenia (Lisman et al. 1998). Dopamine dysregulation in PFC has also been related to WM deficits in schizophrenia (e.g., Arnsten 1998; Braver et al. 1999), so it is possible that NMDA-hypofunction could produce WM deficits both directly and by contributing to dopamine dysregulation.

4.4. Relationships between cognitive coordination and clinical symptoms

At the level of signs and symptoms, fragmentation of mental functions is prima facie evidence of impaired cognitive coordination. At a phenomenological level, this could give rise to experiences in which the individual components of mental or motor activity take precedence over any coherent or integrated pattern of activity. Reviews of phenomenological reports by patients with schizophrenia support this view (Carr & Wale 1986). Reports of fragmented experience can be found throughout the clinical literature, and they suggest that cognitive impairments often involve the reduced coordination of distributed activities.

Cognitive disorganization and thought disorder are more related than are other symptoms to each of the major aspects of cognitive coordination, for example, to sensorimotor gating (Perry et al. 1999), context-sensitivity in language perception (Kuperberg et al. 1998), context-sensitivity in language production (Spitzer et al. 1994), WM for task-relevant information (Cohen et al. 1999a), and knowing what goes with what within the semantic system (Goldberg et al. 1998). The relation of clinical status to perceptual grouping impairments has been studied in detail. They are more pronounced in patients who have been recently hospitalized for acute psychotic episodes compared to patients who have been living in the community for at least six months (Silverstein et al. 1996a). Furthermore, several studies show that patients with poor premorbid social function have more impaired perceptual grouping (Knight 1992; Knight & Silverstein 1998; Silverstein et al. 1996a; 1998c). The Positive and Negative Syndrome Scale (Kay et al. 1987) has been used to relate impairments in cognitive coordination to specific symptom clusters. In one study, the best predictors of performance in a perceptual organization task were determined using a five factor solution (Lindenmayer et al. 1994). Only the cognitive or disorganization factor (consisting of conceptual disorganization, mannerisms and posturing, disorientation, difficulty in abstract thinking, and poor attention) was a significant predictor (Knight & Silverstein 1998). Further evidence comes from a study in which symptoms of the Positive and Negative Syndrome Scale were related to the development of memory representations for configural and nonconfigural stimuli (Silverstein et al. 1998a). Once again, only the cognitive factor significantly predicted task performance. A reduced ability to develop a memory-assisted perceptual organization is therefore related to the disorganization component of symptomatology. A precise psychophysical study (Silver-

stein et al. 2000) also found that a reduced ability to perceive closed contours comprised of noncontiguous Gabor patches was related to higher levels of disorganized symptoms in chronic schizophrenia patients.

Evidence relating abnormal perceptual grouping to disorganized symptoms has also been obtained using the Thought Disorder Index (Solovay et al. 1986). Scores from 21 acutely psychotic schizophrenic patients showed that perceptual organization ability was correlated only with scores of disorganized and associative thought disturbance (Knight & Silverstein 1998). These correlations were not due to a general performance deficit because degrees of disorganized and associative thought disturbance were not associated with baseline levels of perceptual task performance, and because the degree of perceptual organization impairment was not related to overall levels of thought disorder (summed across all four *a priori* factors). Further evidence of a relationship between abnormal perception and thought disorder or disorganized symptoms is that: (1) there is a significant correlation between an index of perceptual fragmentation on the Hooper Visual Organization Test (Lezak 1995) and degree of disorganized thinking (Osborn et al. 1994); and (2) thought disorder correlates with performance on the degraded stimulus version of the continuous performance test, which is a task that involves perceptual grouping (Knight & Silverstein 1998; Nuechterlein et al. 1992; Silverstein et al. 1998b).

5. Cortical rhythms, cognition, NMDA, and psychosis

We argue above that cognitive coordination, NMDA-activity, and psychosis are related. Here we note that evidence relating each of these to high-frequency cortical rhythms strengthens the argument.

5.1. High-frequency rhythms and cognition

Gamma rhythms (30–80 Hz) are currently prominent in electrophysiological studies of cognition (Nunez 2000; Tallon-Baudry & Bertrand 1999). They are relevant to theories of dynamic organization as they reflect synchronized activity that changes on a fast time-scale. They have been related to several aspects of dynamic organization, including Gestalt perception (e.g., Keil et al. 1999), attention (e.g., Tiitinen et al. 1993), and visual search and working memory (Tallon-Baudry & Bertrand 1999). Gamma rhythms are first seen in infant scalp potentials at around eight months of age, which is when other evidence indicates that Gestalt perception shows major developments (Csibra et al. 2000). Though much of this research emphasizes gamma-band activity that is not phase-locked to stimulus events, activity that is phase-locked to stimulation is also relevant (Fries et al. 2001; Haenschel et al. 2000). Finally, coherent dynamics involves more than gamma-band activity (Habeck & Srinivasan 2000). For example, beta rhythms (12–30 Hz) can tolerate longer conduction delays and still synchronize robustly, so they may be involved in coordinating activity between cortical regions (Bressler & Kelso 2001; Bressler et al. 1993; Haenschel et al. 2000). Beta rhythms in the PFC could thus help coordinate activity in posterior cortex that is locally synchronized within the gamma-band (Kopell 2000).

5.2. High-frequency rhythms and NMDA-receptor activity

Mechanisms for the generation and control of high-frequency synchronized rhythms are complex, and not fully understood. As far as we can tell, inhibitory local circuit neurons play a major role in the primary generation of high-frequency rhythms, but NMDA-receptor activity has a role in controlling their strength, duration, and synchronization. Computational modelling clarifies these issues and suggests a role for NMDA-receptors (Jensen et al. 1996; Wright et al. 2001). Direct evidence relating NMDA-receptor activity to high frequency rhythms in auditory cortex (Javitt et al. 1996) was outlined in section 3, but further evidence is also available. Whittington et al. (1997) showed that the transient high-frequency response of hippocampal pyramidal cells to brief input has a component mediated by NMDA and metabotropic glutamate receptors. Funahashi and Stewart (1998) report evidence that the duration of the gamma response of retrohippocampal cells to low-frequency repetitive input depends on NMDA-receptor activation. Faulkner et al. (1998; 1999) show that ketamine and other dissociative anaesthetics can disrupt the synchronization of gamma activity across separate sites and reduce the amount of beta-activity that is induced by gamma activity. Finally, Doheny et al. (2000) found that the NMDA-antagonist ketamine greatly reduced the difference between the gamma responses induced by novel and repeated stimuli in hippocampal slices. This is therefore analogous to the reduced effects of habituation and perceptual learning in schizophrenia.

Thus, although synchronized activity has often been thought to be due primarily to obligatory or driving connections, the above evidence suggests that non-linear contextual connections mediated by NMDA-receptors play an important role in controlling synchronization and thereby helping to coordinate cognitive activity as hypothesized by Phillips and Singer (1997a).

5.3. High-frequency rhythms and schizophrenia

As high-frequency synchronized rhythms are related to both dynamic organization and NMDA-receptor activity, our perspective predicts that they will be changed in schizophrenia. As a first approximation, we can hypothesize that gamma activity will be reduced, particularly in tasks requiring dynamic organization. Low-frequency rhythms may reflect more rigidly specified activity and may therefore be increased. A rapidly growing body of evidence supports these predictions. Using the degraded-stimulus CPT, Hoffman et al. (1996) found reduced gamma activity and increased low-frequency activity in neuroleptic-free schizophrenia patients. Clementz et al. (1997) found evidence relating sensory gating deficits to suppression of gamma activity. Kwon et al. (1999) studied the entrainment of the auditory EEG to clicks presented at 20, 30, or 40 Hz, and found that at 40 Hz this was much less in schizophrenia patients than in controls. Green et al. (1999) interpret the increased effects of visual masking that are associated with schizophrenia as being due to abnormalities in establishing high-frequency rhythms. Kissler et al. (2000) found that, when performing mental arithmetic, schizophrenia patients showed abnormalities in gamma activity, including general decreases of activity in the high gamma-range 60–71 Hz.

The report of exceptionally large 40 Hz rhythms during somatic hallucinations in a schizophrenia patient (Baldeweg et al. 1998) suggests that the hypothesis of reduced high-frequency activity is too simple. Abnormal patterns of high-frequency synchronization across cortical regions may also occur. Furthermore, different schizophrenic syndromes may show different EEG abnormalities. Gordon et al. (2001) related activity in narrow gamma-band (37–41 HZ) responses to target and non-target stimuli in a standard auditory oddball paradigm. Overall, schizophrenic patients showed reduced gamma, but different syndromes were associated with different patterns of abnormality. Reality distortion was associated with increased gamma to targets (which may be an "over-attention" similar to that found by Baldeweg et al.). Psychomotor poverty was associated with reduced gamma to targets. Disorganization was associated with reduced gamma to non-targets, which Gordon et al. interpreted as reflecting a diffuse deficit involving context-sensitivity, with the other two syndromes reflecting distinct patterns of compensatory adaptation to this core deficit. For a more extensive review of evidence relating schizophrenia to changes in high-frequency rhythms see Lee et al. (2003b).

6. Impairments of cognitive coordination are heterogeneous

The depth of the heterogeneity in schizophrenia is unclear. It may be a family of disorders involving impairments of common underlying processes (Andreasen 1999). We will not know whether this is so until we identify any such process. Cognitive coordination is a candidate, and its disorders may be heterogeneous in several senses. They may be heterogeneous in that different aspects of coordination may be impaired to different extents and in different combinations. They may also be heterogeneous in the sense that disorders of coordination may be combined with disorders of various other aspects of mental function to produce differences both within and between classically defined psychiatric conditions.

Our hypothesis does not imply that schizophrenia is a homogeneous condition, but leaves much room for heterogeneity, both of neuropathology and of symptomatology.[4] It suggests that some of the symptoms associated with schizophrenia are a direct consequence of NMDA-hypofunction, and that others are a consequence of associated pathophysiology, such as dopamine dysregulation or neuronal degeneration (Jentsch & Roth 1999). We have focused on the attempt to characterize those that are directly due to disorders of coordination. Some non-psychotic visual disorders show that such disorders can be very specific. One example is strabismic amblyopia, which involves both impaired perceptual grouping (Polat et al. 1997) and impaired neuronal spike synchronization (Roelfsema et al. 1994). Impairments of particular aspects of cognitive coordination may also occur in some psychiatric disorders. For example, impairments to sensory gating can occur in mania (Franks et al. 1983). Impairments of many different aspects of cognitive coordination can also occur together, however, as in PCP-psychosis. The covariance of many aspects of cognitive coordination with thought disorder in schizophrenia also suggests that they are often jointly impaired.

The covariance of impairments in coordination with thought disorder does not imply that they are unrelated to other symptoms. First, NMDA-antagonists can rapidly induce hallucinations, delusions, and negative symptoms in normal volunteers, and profoundly exacerbate all of these symptoms in schizophrenic patients (Jentsch & Roth 1999). Second, in patients whose glycine levels are initially sub-optimal, glycine agonists (which then facilitate NMDA-channel opening) can improve negative symptoms (Goff et al. 1999; Heresco-Levy et al. 1999). Third, poor motor learning discriminates children at risk of developing schizophrenia from normal children (Mednick & Silverton 1988), so disorders of motor coordination may be related to disorders of cognitive coordination. This is consistent with neurophysiological studies of motor cortex showing that spike synchronization occurs during normal sensorimotor coordination (Murthy & Fetz 1996; Roelfsema et al. 1997), and with cognitive studies indicating that feature binding mechanisms are operative in action planning (Stoet & Hommel 1999). Fourth, Carr and Wale (1986) present detailed arguments for viewing many hallucinations and delusions as compensatory adaptations to impairments of the processes that organize information into coherent wholes prior to the allocation of attention. Finally, internally generated mental activities also need to be linked to their source (Frith 1992), and if this linking fails, then various hallucinations and delusions may occur.[5]

Impairments of any particular aspect of cognitive coordination can also vary in severity. Consider perceptual organization. Patients with histories of poor premorbid social functioning show abnormalities that patients with good premorbid histories do not (Knight 1984; 1992; Knight & Silverstein 1998; Silverstein et al. 1996a). This suggests that some perceptual abnormalities reflect more severe disability. This is supported by evidence that perceptual organization abilities on admission to a long-term psychiatric rehabilitation unit significantly discriminated between patients who could be discharged within three years from those needing longer hospitalizations (Silverstein et al. 1998e). Impairments of perceptual organization may therefore occur at different levels of severity (Silverstein & Schenkel 1997). Subtle sensory gating abnormalities may also occur in the absence of psychosis because failure to attenuate the P50 psychophysiological response to the second of two auditory stimuli is distributed across affected and unaffected relatives of schizophrenic patients in a pattern consistent with autosomal dominant transmission (Adler et al. 1998b). More severe dysfunction of more aspects of perceptual processing may occur during states of acute psychosis. Evidence for this is that perceptual grouping disturbance is more prevalent among acutely psychotic poor premorbid inpatients than among outpatients with schizophrenia who have poor premorbid histories (Silverstein et al. 1996a), and that degree of perceptual organization disturbance in schizophrenia patients is significantly correlated with severity of disorganized symptomatology (Knight & Silverstein 1998; Silverstein et al. 1998a; 2000). We therefore conclude that impairments of cognitive coordination can range from mild impairments of a few aspects to severe impairments of many.

The neurodevelopmental model of Hoffman and McGlashan (1993) may be useful in explaining why perceptual grouping impairments are found mainly among schizophrenia patients with poor premorbid functioning, and among such patients when they are exhibiting psychotic

symptoms. Noting evidence of exaggerated developmental neuronal pruning, they proposed that corticocortical connectivity may be abnormal in schizophrenia in one of three ways, depending on the number of initial connections and the amount of later pruning that occurs. Low initial connectivity combined with normal pruning would lead to an early age of onset, whereas a normal amount of initial connectivity combined with abnormally extensive pruning would lead to good premorbid functioning and a fast onset of psychosis. This is consistent with the view that more global adaptive difficulties occur as a result of reduced density/connectivity earlier in life, and that more specific and serious manifestations of impaired connectivity and coordination occur later, when further reductions in connectivity create the potential for psychosis to emerge (Silverstein & Schenkel 1997). These more serious manifestations of impaired connectivity and coordination could include both disorganized symptoms and the impairments in perceptual grouping with which they are associated (Knight & Silverstein 1998; Silverstein et al. 1996a; 1998a; 2000).

Cognitive disorganization and disorders of holistic Gestalt processing, may also be involved in other conditions, such as autism and some other neurodevelopmental disorders.[6] The tendency for autistic subjects to process inputs as sets of independent parts, rather than as coherent wholes, has been clearly shown in various cognitive domains, including visual perception, visuospatial construction, and language processing (Frith & Happé 1994; Happé 1997; 1999). Furthermore, a mild variant of this cognitive style is seen in the parents of children with Asperger's Syndrome (AS), and is more characteristic of males than of females (Baron-Cohen & Hammer 1997). A recent study found that of fourteen men diagnosed as autistic, seven met criteria for schizophrenia of the disorganized type (Konstantareas & Hewitt 2001). Genetically specified variations in the strength of coordinating neuronal interactions may therefore play an important role in producing different cognitive phenotypes, and this is in agreement with Karmiloff-Smith's (1998) argument that many neurodevelopmental disorders arise from impairments of cellular-level processes that are common to many brain regions, rather than to impairments that are localized in high-level cognitive modules with particular roles that are genetically prespecified.

7. The hypothesis of impaired coordination is related to several other theories

Jansen and Faull (1991) note that it is impossible to propose a model of schizophrenia without ignoring most of the data. It is also impossible to do so without ignoring most of the other theories! Though we have focussed on coordinating interactions within the cortex, we assume that dynamic organization and contextual disambiguation are also relevant to the function of other brain regions such as the basal ganglia, the limbic system, thalamus and cerebellum. All of these have been implicated in schizophrenia, and have been emphasized by many different theories of its pathophysiology. Though there is no space to discuss them here, our working assumption is that the coordination of activity, mediated in part via NMDA channels, is as important to their function as it is to that of the cortex.[7]

As our discussion of relevant theories is necessarily selective, we emphasize only those that have led us to the perspective advocated. We discuss three groups of theories that have for the most part been developed separately, hoping to show ways in which they are mutually supportive.

7.1. Theories emphasizing disconnection between cortical regions

The disconnection hypothesis is built on conceptual foundations that combine ideas developed within the fields of theoretical neurobiology, cognitive neuropsychology, and neuroimaging (Dolan et al. 1999; Friston 1999). Schizophrenia is interpreted as arising from malfunctions of the dynamic interactions between cortical regions. It therefore contrasts with classical neuropsychological syndromes in that the disorder is not localized within specialized regions. The disconnection is not primarily anatomical but functional, that is, it is a disorder of the effective connectivity that mediates dynamic interactions. These change both on long and on short time-scales. The former relates to learning, and the latter to processing, and in particular to the dynamic modulation of effective connectivity. Symptoms of reality distortion and disorganization are seen as arising from a failure of the dynamic organizational processes that integrate activity across different regions. One example is the explanation of verbal hallucinations as a failure in self-monitoring, as suggested by Frith (1992) and outlined in section 6. Another is that delusions of alien control can be seen as a failure to integrate the intention to act with the perceptual registration of the consequences of that action (Friston 1999). In relation to the neuropathophysiology it is suggested that changes in effective connectivity arise in part from over-activity of dopamine D1 receptors in the anterior cingulate gyrus (Dolan et al. 1999).

There are several similarities between this hypothesis and that presented here. (1) Both emphasize the distinction between functional segregation and functional integration (Tononi et al. 1994). (2) Both emphasize dynamic interactions between cortical regions. For example, the explanations for verbal hallucinations and alien control just outlined depend upon what we call dynamic grouping. (3) Both distinguish between linear and non-linear interactions, with the form of the non-linear interaction that they use being remarkably similar (compare Equation 2 of Friston et al. 1995 with Equation 2 of Phillips et al. 1995). In both approaches, this non-linear interaction is interpreted as modulating the response of cortical neurons to their inputs from other sources. (4) Both emphasize that long-term changes to synaptic connectivity result from changes to the dynamic modulation of short-term processing. Indeed, learning was the initial focus of the Coherent Infomax theory (Phillips et al. 1995), where analytically derived rules for synaptic plasticity were used for the contextual guidance of learning, and were shown to have detailed similarities to a form of synaptic plasticity for which there is physiological evidence (Phillips & Singer 1997a). For an improved and even more physiologically plausible version of these learning rules, see Körding and König (2000).

There are also differences between the disconnection hypothesis as developed so far and the perspective presented here. (1) Friston et al. emphasize faulty modulation of long-term plasticity, whereas we primarily emphasize the immediate effects of modulatory interactions on the dynamic organization of processing, and interpret the longer-term changes in connectivity as being dependent on that.

(2) They emphasize faulty interactions between cortical regions, whereas we also emphasize interactions within regions. (3) Though they distinguish between modulatory and obligatory connectivity (Friston et al. 1995), they do not emphasize the primary role of the modulatory connections in the dynamic coordination of activity, whereas we do. (4) As a consequence of the preceding, we put more emphasis on the NMDA-receptor and its possible pathologies than they do. Overall, the similarities are more fundamental than the differences, so we see the two approaches as complementary.

7.2. Theories emphasizing impairments in cognitive coordination

Our perspective extends the pioneering work of the Gestalt psychologists and Gestalt theory-influenced psychiatrists. For Matussek (1952/1987), the perceptual world of schizophrenia patients was characterized by a splitting of individual perceptual components from their natural context. This allowed normally incidental objects in the environment to take on unusual significance, and could relegate important stimuli to background status. Matussek reported cases of intense attentional focus on environmental details, and compared this to the heightened sense of an object that can occur under the influence of psychotomimetic agents such as mescaline. Experiences of attentional alteration, reduced awareness of surroundings, and an altered sense of reality and the self have been reported among nonpatients during states of "absorption" (Tellegen & Atkinson 1974), and similar states occur in schizophrenia (Fisher 1976a; 1976b; Silverstein 1988).

A major difference between the transient states and psychotic episodes in schizophrenia is that the latter are not under the control of the individual, and thus have more serious long-term effects. These include giving atypical meanings to stimuli and the formation of new perceptual contexts that would further pull the patient away from reality. A classic example of this process is provided by one of Matussek's patients: "these objects seemed altered from the usual. They did not stand together in an overall context, and I saw them as meaningless details" (Matussek 1952/1987). Further research supports several of Matussek's hypotheses. For example, he hypothesized that the contextual weakening would vary depending on the severity of the illness. This has been confirmed by evidence reviewed earlier (Knight & Silverstein 1988; Silverstein et al. 1996a; 1998a; 1998c; 1998e). Matussek also believed that awareness of appropriate contextual relationships could be brought about by drawing attention to relevant information, but that this awareness of context would be of only limited duration and would soon disintegrate. The ability to improve perceptual organization and other forms of context processing in schizophrenia through attentional manipulations has now been demonstrated experimentally (Silverstein et al. 1996a, Study 2), as has the temporary nature of the effect (Cromwell 1975; Kaplan 1974; Nuechterlein 1977).

A more recent view of schizophrenia based on similar principles is that of Carr and Wale (1986), who hypothesized that there are basic deficits in processes that organize both externally and internally generated activity. They view much of schizophrenic disorganization as reflecting the consequent failure to impose order on experience. They see a subtle impairment in cognitive organization as a stable aspect of the illness, with more serious manifestations being due to sensory gating impairments becoming so severe that a system already deficient in organizing input is then overwhelmed by an even greater amount to be processed.

Many theories emphasize specific deficiencies in the use of context; for example, Gray et al. (1991) suggest that a key cognitive deficit in schizophrenia consists in the failure to relate specific associations to the context in which they occur, thus leading to impaired determinations of "relevance." Context plays a central role in the work of Cohen and colleagues (Braver et al. 1999; Cohen & Servan-Schreiber 1992; Cohen et al. 1999a), who show how impairments in the CPT, the Stroop task, and lexical disambiguation could be due to malfunction of a WM system in the PFC. In an early version of their theory, these impairments were modelled as arising from reduced gain of units in a component of the model interpreted as being in the PFC (Cohen & Servan-Schreiber 1992). In a later version, they are modelled as arising from increased noise levels in mesocortical dopamine (Braver et al. 1999). In both cases, the changes are hypothesized to arise from reduced dopaminergic modulation in the PFC. Our work builds in part upon theirs, but with important differences. Both approaches combine psychological, biological, and computational perspectives in their attempts to understand cognition in schizophrenia; but we emphasize general principles derived from the Coherent Infomax theory of cortical computation (Phillips & Singer 1997a), and they emphasize connectionist simulations of performance in particular cognitive tasks. [For a detailed description of relations between computational theory and computational modelling, see Phillips and Singer (1997b, Table R2).]

Both approaches hypothesize that many cognitive deficits and clinical symptoms arise from changes to a few basic mechanisms involving context. In both, this is thought of as "information that is relevant to but does not form part of the content of the response" (Cohen & Servan-Schreiber 1992, p. 46), but whereas we see this as a basic aspect of cortical computation in general, they emphasize only task-relevant information stored in a WM component of PFC. The importance of the distinction between working memory and sensory levels of processing is not in question, having been clearly demonstrated long ago (Phillips 1974). The point we emphasize here is that contextual interactions are relevant to all levels. In support of this view we emphasize contextual interactions within perception. An important difference is therefore that Cohen et al. identify context with a particular set of representations, whereas we identify context with a widely distributed class of synaptic interactions. Another difference is that we see dynamic grouping as a fundamental form of coordination, and this relates our approach in very specific ways to high-frequency cortical rhythms as outlined in section 5. Finally, Cohen et al. emphasize dopaminergic modulation of explicit task-related information in PFC, whereas we emphasize NMDA-hypofunction. These are compatible. Indeed, they must be complementary, as the neurotransmitter systems involved are very different, but both have modulatory or coordinating functions. A major goal for future research is therefore to discover how they are combined.

7.3. Theories emphasizing NMDA-hypofunction

Several recent theories of pathophysiology in schizophrenia emphasize NMDA-hypofunction (Coyle 1996; Ellison 1995;

Hoffman & McGlashan 1993; Javitt & Zukin 1991; Jentsch & Roth 1999; Olney & Farber 1995; Tamminga 1998), but they rarely relate that to cognitive coordination, and they do not emphasize the ability of NMDA-channels to provide gain-control through voltage-dependence. One research group that does both, however, is that of Javitt and colleagues. They interpret their studies of primary auditory cortex (Javitt et al. 1996) as showing that NMDA-channels are involved in modifying the strength of response to infrequent deviant stimuli within a sequence of repetitive stimuli. They note that this modification involves the contextual component of response rather than the obligatory stimulus-induced response, and interpret it as showing how a stimulus of one type can alter the response to a related but different stimulus. This component therefore provides a clear example of what we call contextual coordination. Javitt et al. (1996) also suggest further ways in which the role of inhibitory interneurons can be incorporated into an account of NMDA function and malfunction. Furthermore, although they demonstrate malfunction of preattentive processes in sensory cortex, they hypothesize, as we do, that analogous malfunctions can also apply to higher cognitive processes. Their studies using the CPT and mismatch negativity in both schizophrenia (Javitt et al. 2000) and in healthy volunteers (Umbricht et al. 2000) provide strong support for this hypothesis.

8. Issues arising

The perspective advocated here has implications for conceptions of cognitive neuropsychiatry, which when modelled too closely on cognitive neuropsychological studies of the effects of brain damage tends to neglect cellular physiology and neuropharmacology. This stands in stark contrast to the central role of pharmacotherapy in psychiatric practice. From our perspective, cognitive neuropsychiatry has much to gain by relating psychological disorders to neuroscience at the cellular level. Our perspective also encourages the application of new analytic techniques to neuroimaging data. Studies of cerebral blood flow have associated symptoms of disorganization with decreased perfusion in the right ventral prefrontal cortex and insula and with increased perfusion in the right anterior cingulate gyrus (Liddle et al. 1992). These are not the regions expected to be involved in the perceptual disorders outlined above. Failure to find changes in gross activity in perceptual regions is not incompatible with the hypothesis of impaired perceptual coordination, however, because both contextual disambiguation and dynamic grouping could occur with little or no change in gross activity. This emphasizes the need to consider not just gross activity within each region, but also its fine spatiotemporal structure both within and between regions. Techniques for imaging the extent to which brain regions interact (Tononi et al. 1998a) may therefore be relevant to psychosis, particularly when applied to data with high temporal resolution. Similarly, techniques for imaging synchronization on a fast time scale using EEG data (Phillips & Pflieger 2000; Tallon-Baudry & Bertrand 1999), and for distinguishing modulatory from obligatory intracortical interactions using fMRI data (Friston et al. 1995), may also have much to contribute.

The central hypothesis examined in this target article is that disorganization in some forms of psychotic cognition arises from reduced ion-flow through the NMDA family of glutamate receptors. Though both the cognitive and the neuropharmacological components of this argument are currently receiving much attention and support, neither is yet clearly established, and the wide-ranging implications of their mutually supportive relationship have been little discussed. We are well aware that our argument goes beyond what is currently widely agreed, and four central issues for commentary arise. (1) Does reduced ion-flow through NMDA-channels play a crucial role in the pathophysiology of cognitive disorganization in schizophrenia, and, if so, how does that relate to dopamine dysregulation and other pathophysiologies more widely thought to be involved in the disorder? (2) Is a reduction in context-sensitivity central to many of the cognitive impairments known to be associated with schizophrenia? Some investigators have suggested that context-sensitivity is not reduced in schizophrenia, but increased (David 1994). Should further tests show this to be so, then that will disprove what we advocate. (3) Does reduced flow through NMDA-channels play a central role in producing disorders of context-sensitivity? If it is shown that both occur, but apply to different patients, then that will be strong evidence against the position we advocate. (4) Does cognitive disorganization in PCP-psychosis provide evidence that normal cognition depends upon coordinating interactions that are implemented via NMDA-receptors?

Several closely related issues arise, the most important being as follows. (1) Can impairments of a fundamental underlying process in schizophrenia account for disorganization across cognitive, behavioral, and symptomatic domains, or are deficits in these domains best seen as being independent and capable of occurring in many different combinations? (2) Insofar as contextual interactions are involved in these disorders, is the relevant context only that which is provided by preceding information held in a working memory that is located in prefrontal cortex, or is it much wider than that, including current stimulus context and part-whole relationships? (3) Clinically, semantic associations are seen to be much less focussed in thought disordered patients, and this may be reflected by greater indirect semantic priming (Spitzer et al. 1993). How can our perspective be related to this? The first thing to note is that semantic associations require compositionality, which can be implemented via the dynamic grouping processes we have emphasized. These depend on contextual interactions, and mediated or indirect contextual interactions require primary input to the mediating items (Kay et al. 1998). Thus, if primary sources of activation, for example, from memory retrieval processes, noise, or other sources of activation is less focused in thought disorder, then more indirect associations can be predicted. (4) NMDA-receptors are widely thought to play a major role in learning, but not in ongoing processing, so how well supported is our claim that this view is mistaken and that NMDA-receptors also play a crucial role in ongoing processing? (5) The voltage-dependence of NMDA-channels is usually ignored in discussions of their role in schizophrenia and PCP-psychosis, so how justified is our emphasis upon this property? (6) Are any other receptors plausible candidates for the role of implementing coordinating interactions between the pyramidal cells whose activity embodies our cognitive contents? (7) Which clinical symptoms are likely to be due to reduced context-sensitivity, and which are not? (8) How similar are

the cognitive deficits that occur in PCP-psychosis and schizophrenia? (9) Is there a spectrum of cognitive phenotypes characterized by genetic variations in the balance between locally independent processes and context-sensitive holistic Gestalt interactions? (10) Is there evidence for underactivity of NMDA receptor channels in any other disorders involving cognitive disorganization? (11) Is the molecular and regional diversity of NMDA receptor channels (Kutsuwada et al. 1992) crucial, and is NMDA dysfunction limited to the cortex or does it also occur in other brain regions? (12) What pathophysiologies other than NMDA-hypofunction can impair the specific class of neuronal interactions that underlie cognitive coordination? Though we have focussed on NMDA-hypofunction, they could also be disrupted in other ways, such as via abnormal pruning (Hoffman & McGlashan 1993; McGlashan & Hoffman 2000), or via impaired consolidation of coordinating connections due to abnormal input during development, for example. (13) Do high-frequency rhythms provide a useful window on processes of dynamic organization and their impairment in schizophrenia? (14) Do postmortem and other studies indicate that cognitive disorganization is associated with reduced lateral and descending long-range connections of the kind that mediate contextual coordination via NMDA-receptors? (15) Why do some antipsychotic medications reduce cognitive disorganization? One recent review (Mechri et al. 2001) concludes that clozapine significantly reduces the ketamine-induced positive symptoms in schizophrenic patients. Another concludes that the effects of some atypical antipsychotics such as clozapine and olanzapine on NMDA receptors differentiates them from typical antipsychotics such as haloperidol (Goff & Coyle 2001). It is therefore possible that some widely used antipsychotics enhance NMDA-receptor activity and thus reduce cognitive disorganization. If so, then agents more specifically designed to enhance NMDA activity, perhaps via the glycine modulatory site, may be even more beneficial. (16) Finally, how widely supported is our view that neuroscience at cellular and molecular levels should play a far greater role in cognitive neuropsychiatry than it has done so far in cognitive neuropsychology?

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NOTES

1. Consider illusory contours. Prima facie, this seems to be a case where context provides primary drive as it produces signals for things that are not there. This is clearly different to the examples shown in Figure 1a, right-most column, where context does not produce the perception of absent things. One way to handle such exceptions is to say that, to the extent that surrounding items produce primary drive, then they are, by definition, not acting as context. This view could be tested for coherence with the rest of our perspective in various ways, including investigations of the RF inputs to cells in visual cortex to see whether they included input from surrounds that produce illusory contours. Note that this is not merely a matter of finding out whether surrounds influence the activity of cells in visual cortex (we know that they do), it is a matter of finding out whether that influence is driving or modulatory. It could be both. Another way to view such exceptions is therefore to see them as the faint ghosts of modulatory inputs that in these exceptional cases produce output, possibly by amplifying selected components in background or noise activity. This latter view implies that the function of processes reflected in illusory contours is to amplify relevant but weak evidence that is actually present, rather than to signal the presence of absent things.

2. The creation, maintenance, and use of strategies that meet longer-term goals of the organism as a whole are computationally feasible because they are performed by systems that do not need to coordinate all the local details. Psychology and neurobiology have for many years provided evidence of such strategic or executive functions (Baddeley 1996; Fuster 1997; Miller & Cohen 2001; Shallice 1988). Functional neuroimaging now adds to that evidence (Posner & Raichle 1994), and shows that new theories are required to improve our conceptions of executive functions (Grafman et al. 1995). They involve several distinct sub-divisions of the PFC and anterior cingulate gyrus which operate via interactions with limbic, striatal, and posterior cortical regions. Though no definitive taxonomy is yet agreed, several classes of executive function are often postulated: modulation of schemas or routines in lower-level systems, including the inhibition of dominant response tendencies when they are inappropriate in the current context (Frith 1992; Liddle & Morris 1991; Shallice 1988); modulation of perception and the control of attention in visuospatial and other modalities (Posner & Raichle 1994); the maintenance or use of information in components of working memory (Goldman-Rakic et al. 2000); the formation and use of contextual associations in episodic and source memory (Janowsky et al. 1989: Shallice et al. 1994) and the assignment of affective significance (Damasio 1994; Petrides 1994; Robbins 1996); and the creative manipulation of information to solve novel problems (Owen 2000; Robbins 1996; Shallice & Burgess 1996). Anatomical localization within PFC depends on semantic content, for example, with some parts being specialized for phonological information and others for visuo-spatial information (Goldman-Rakic et al. 2000). Different subdivisions of PFC may also be specialized for some executive functions rather than others. For example, some may be specialized for selectively disinhibiting lower-level routines, and others for the creative manipulation of information (Owen 2000).

3. Another aspect of executive function may be the gating of input to a component of WM in PFC that holds contextual information (Braver et al. 1999). It was clear from the original studies of visual short-term memory that interference due to subsequent activities was a major cause of short-term forgetting, and that central executive functions are important in controlling that interference (Phillips & Christie 1977). The theory of Braver et al. (1999) offers a connectionist model that relates such interference to the gating of access to WM in PFC.

4. The rich anatomical complexity of the glutamatergic system greatly increases the scope for heterogeneity. NMDA-channels are built from varying combinations of five different sub-units with varying regional distributions, developmental histories, and physiological properties (Watanabe et al. 1992). Different disorders, including those with genetic origins, could therefore effect these different subtypes of NMDA receptor in different ways; for example, schizophrenia is associated predominantly with abnormalities of the obligate NMDA-receptor subunit (Meador-Woodruff & Healy 2000). The close interactions between the NMDA and dopamine systems implies that a primary pathology in either could lead to dysregulation of the other. Another possible source of heterogeneity is that the amount of neurodegeneration may depend upon whether glutamatergic overactivity due to

reduced NMDA-channel activity on inhibitory cells outweighs underactivity due to reduced NMDA-channel activity on glutamatergic cells. This is compatible with evidence for cases of schizophrenia both with and without progressive degeneration (Benes & Coyle 1998).

5. When patients experience verbal hallucinations they do not know that the words they experience are due to activity in those other parts of their cognitive system that generate things to be said (Frith 1992). Such hallucinations are possible because the sub-systems that instantiate the phonological and semantic forms of words can be activated by input from any of several different sources, some internal, some external. To signal the origin of activity within them on any particular occasion, that activity must be dynamically linked to the activity from which it arose on that occasion. Failure of this dynamic linking could produce the strange experience of having words in mind, but not as part of a larger pattern of activity that links them to their origin in other brain regions on that occasion. Verbal activity might then be experienced as coming from outside the self, and delusional beliefs might then reflect attempts to account for this experience.

6. Silverstein and Palumbo (1995) describe similarities between schizophrenia and nonverbal perceptual-organization-output disability, which is a severe form of nonverbal learning disability thought to fall within the autism spectrum (Rourke 1982). They suggest that this disorder also involves impaired stimulus organization mechanisms, and that studies of such disorders could compliment high-risk studies in the attempt to uncover the aetiology of schizophrenia. Furthermore, some learning disabled individuals have deficits in backward masking (Blackwell et al. 1983) and span of apprehension tasks (Tarnowski et al. 1986), which are often thought to be vulnerability markers for schizophrenia. Thus, there is evidence of common cognitive impairments in schizophrenia and some other neurodevelopmental disorders. It is not the case that all of these populations perform similarly simply by virtue of a general intellectual impairment. Certain developmental disorders exhibit a very different pattern of cognitive deficits. For example, patients with Williams Syndrome show increased rather than decreased global processing (Pani et al. 1999), when tested on the same perceptual organization task as used with schizophrenic patients by Silverstein et al. (1996a). Much may therefore be gained by comparing these disorders using relevant process-oriented designs (Knight 1992; Knight & Silverstein 1998).

7. Discussing the role of the thalamus in the pathophysiology of schizophrenia, Patterson (1987) concludes "If one were to single out a brain structure that displayed the possibility for central 'timing' functions in brain, it would most likely be the thalamus." The basal ganglia are also often implicated in schizophrenia (Robbins 1990). Graybiel (1997) argues that just as they contribute to the coordination of motor output so they may also contribute to the coordination of cognitive activity. She argues that in both cases this coordination involves dynamic binding through the synchronization of firing patterns so as to produce appropriate and precisely timed sequences of activity. In their review of the functional architecture of the basal ganglia, Alexander and Crutcher (1990) conclude that "the functional integration that is widely assumed to occur within these circuits may prove to be based less upon the spatial convergence of functionally disparate pathways than upon the temporal coincidence of processing within pathways whose functional segregation is rather strictly maintained" (p. 270). All these views are highly consonant with that proposed here. One function of the limbic system is thought to include putting things in context while maintaining their individual identities, so that too, may involve the formation of contextual associations that are implemented in part by NMDA-receptors, which are particularly dense in the hippocampus.

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The ketamine model for schizophrenia

Murray Alpert and Burt Angrist

Department of Psychiatry, NYU School of Medicine, New York, NY 10016.
murray.alpert@nyu.edu

Abstract: This commentary compares clinical aspects of ketamine with the amphetamine model of schizophrenia. Hallucinations and loss of insight, associated with amphetamine, seem more schizophrenia-like. Flat affect encountered with ketamine is closer to the clinical presentation in schizophrenia. We argue that flat affect is not a sign of schizophrenia, but rather, a *risk factor* for chronic schizophrenia.

The Phillips & Silverstein (P&S) target article provides striking evidence for the explanatory power of drug models of psychotic psychopathology, although the paper is broader than the ketamine story, touching on clinical, cognitive, electrophysiologic, neuroanatomic, and other domains. We will focus on the clinical aspects of drug models of psychosis and compare ketamine with amphetamine, with some consideration of hallucinatory processes and loss of insight. In addition, we will touch on questions related to the role of flat affect. The target article should facilitate empirical study of important questions such as differences between ketamine and competing drug models.

At present, a number of drugs tied to different neurotransmitters have been shown to provoke psychotic symptoms. Early on, LSD produced considerable interest because of the tiny dose required for an induction. It was possible to imagine that a metabolic error could produce an endogenous intoxicant. Mescaline attracted interest because of its structural similarity to dopamine, and the authority of the transmethylation hypothesis. Neither LSD nor mescaline produced a clinical presentation that had the "look and feel" of schizophrenia. It appeared that different transmitters might provide some specificity for the different psychoses: Prolonged exposure to steroids could produce states that mimicked manic psychoses, and a ditran induction shared characteristics with the alcohol-withdrawal psychoses (Alpert et al. 1970).

The amphetamine model psychosis provides the "look and feel" of paranoid schizophrenia and nests nicely with the dopamine hypothesis of schizophrenia. Because of the risk of cardio-toxic effects, the rate of dosing of amphetamine must be slow, and the rate and duration of dose increase may be important for the amphetamine model (Alpert & Friedhoff 1980). Many of these issues appear accessible to empirical study within the conceptual framework of the P&S article. The amphetamine model seems more attractive than ketamine for a number of reasons. A model should demonstrate a schizophrenic presentation without altering consciousness, and ketamine is an anesthetic. It has a narrower range of action below a threshold for clouding.

In addition, the hallucinatory phenomena with ketamine are less compelling: The hallucinations are more mixed with illusions and there is a shift to visual compared with auditory changes. In surveys of hallucinations in schizophrenic patients (Alpert & Silvers 1970), about 50% of the patients reported auditory hallucinations and about 20% reported visual hallucinations, and all of the patients with visual hallucinations also had auditory ones. Schizophrenic hallucinations are primarily verbal, of high intelligibility, and give the impression of "thoughts becoming audible." The alcoholic auditory hallucinations resemble "sounds becoming