The organized complexity of mental life depends on mechanisms for context-sensitive gain-control that are impaired in schizophrenia

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Abstract

There is rapidly growing evidence that schizophrenia involves changes in context-sensitive gain-control. Here we review evidence for five central hypotheses that are supported by this evidence. First, context-sensitive gain-control is fundamental to brain function and mental life. Second, it occurs in many different regions of the cerebral cortex of many different mammalian species. Third, it has several computational functions, each with wide generality. Fourth, it is implemented by various mechanisms at cellular and circuit levels. Fifth, impairments of context-sensitive gain-control produce the well-known symptoms of schizophrenia and change basic processes of visual perception. These hypotheses suggest why disorders of vision in schizophrenia may provide insights into the nature and mechanisms of impaired reality testing and thought disorder in psychosis. They may also cast new light on mental function and its neural bases. Limitations of these hypotheses, and ways in which they need further testing and development, are outlined.

Keywords: cognitive coordination, context-sensitivity, gain-control, perceptual grouping, coherence, vision, schizophrenia, cortical computation

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1. Introduction

It has been argued that gain modulation, or gain-control, is a major principle underlying brain function (e.g. Salinas and Sejnowski, 2001, Chance et al., 2002). Put simply, gain-control changes the rate at which a neuron's output increases with the strength of the driving inputs to which it is selectively tuned. This suggests that neurons have two classes of input: one specifying selectivity and the other controlling gain. There is evidence that the former tend to be few but strong whereas the latter includes many that are individually weak. Gain-controlling inputs include both the classical neuromodulators and the much more locally specific gain-control with which we are predominantly concerned here. To indicate our focus on the latter we will refer to it as context-sensitive gain-control. The distinction between drive and gain-control will be developed further in the following sections in relation to five central hypotheses. First, context-sensitive gain-control is fundamental to brain function and mental life. Second, it occurs in many different regions of the cerebral cortex of many different mammalian species. Third, it has several computational functions, each with wide generality. Fourth, it is implemented by various mechanisms at cellular and circuit levels. Fifth, impairments of context-sensitive gain-control produce the well-known symptoms of schizophrenia and change basic processes of visual perception. To the extent that schizophrenia arises from widespread impairments of context-sensitive gain-control, insights gained from studying it can also inform our basic understanding of brain function and mental life in general.

Our perspective on these hypotheses is guided by several meta-theoretical attitudes and working assumptions. One is that our perspective is resolutely multi-disciplinary. Schizophrenia involves circuit and cellular pathologies with great consequences for mental life. We do not see how they can be understood without a theory of brain function and its pathologies that adequately relates microscopic and macroscopic levels. Of course that is a challenge that dwarfs our attempt to meet it, but try we must. In their influential normalization model of attention Reynolds and Heeger (2009) say that they offer a computational theory while remaining agnostic about biophysical mechanisms. They note that the latter will become increasingly important, however, as neuroscience continues to reveal ever more about the underlying circuitry and cellular mechanisms. That level is clearly relevant to the issues considered here because so much is already known about the neurobiological bases of schizophrenia spectrum disorders. Perspectives that unify findings from computational, psychological, and neurobiological approaches are more likely to advance our understanding than any that is based on only one of them.

We assume that there are two-way causal interactions between macroscopic events at a psychological level and microscopic events at a cellular level. Events initiated at a psychological level can have great consequences at the cellular level, and vice versa. We assume genetic susceptibility to play a major role in schizophrenia, but progression to a full psychosis also depends on many other contingent events, including epigenetic factors and environmental stressors. Our concern here is not with aetiology, but with the nature of the psychotic state to which various paths may lead. Our working assumption is that characterization of that state at the level of pathophysiology may be simpler than at any other.

We are well-aware that context-sensitive gain-control takes many different forms, including those implemented via the classical neuromodulators that have long been associated with the psychoses. Nevertheless we focus on gain-controlling interactions within and between cortical glutamatergic and GABAergic neurons for reasons that will be made clear below. They are essentially that it is only those neurons that convey the detailed cognitive content whose coherence is compromised in schizophrenia. It is not the inputs from sub-cortical neuromodulatory systems that convey that content, even though they do have modulatory effects on the intra-cortical interactions that do. Furthermore, there is ample evidence that the pathophysiology of schizophrenia involves glutamatergic and GABAergic interactions, as made clear below.

We also assume that impairments at the circuit and cellular levels are likely to be subtle, such as those related to differences between subtypes of cortical neuron or synaptic receptor that are

quantitatively small but nevertheless with important implications for mental life. For example, there are various subtypes of the NMDA class of synaptic receptors for the main excitatory cortical neurotransmitter, glutamate, with the 2A and 2B subtypes being the most common in cerebral cortex. Small parametric differences in their biophysical properties suggest that the 2A subtype is better suited to operate on signals with high temporal precision. In addition, there is evidence that adolescence is associated with dramatic changes in NMDA-receptor (NMDAR) distribution and subtypes (Wang and Gao, 2009), including a switch from the 2B to the 2A subtype (Liu et al., 2004). This suggests that disorders with an adolescent onset might be related to such subtle differences, particularly as changes in temporal precision are also implicated in the pathophysiology of schizophrenia.

As context-sensitivity is central to our hypotheses we must also make clear what we mean by 'context'. Some influential researchers identify 'context' with the information in working memory (e.g. Cohen and Servan-Schreiber, 1992; Gonzalez-Burgos and Lewis, 2008; Lewis, 2012). From our perspective that is far too narrow a conception, and a broad but rigorous formal definition of context will be given in the following section. Given the depth and rigour of analyses of context-sensitivity in perception (e.g. Schwartz et al., 2007), and the breadth of the evidence for its involvement in various cognitive functions and their impairments (e.g. Phillips and Silverstein, 2003), we see no justification for ignoring the broader conception of context that we espouse. We therefore predict that papers in this *Frontiers* Research Topic will report further impairments of context-sensitive perception for which there is no plausible explanation in terms of impaired working memory or executive functions.

A smaller difference of terminology should also be noted. Previous papers, by ourselves and others, have distinguished gain-control from dynamic Gestalt grouping or 'integration'. Here we use the phrase context-sensitive gain-control to cover both, for reasons that will be made clear below. They are essentially that grouping can be seen as a form of context-sensitive gain-control on a fast time-scale, and that it may use essentially the same mechanisms as other forms of gain-control. The close relations between grouping and those other forms of gain-control are clear in the similar dependence of contour integration and flanker facilitation on collinearity. Further support for this proposed taxonomy is provided by evidence that in schizophrenia there are clear deficits in both contour integration (Silverstein et al., 2009) and flanker facilitation (Must et al., 2004).

We do not provide a comprehensive review of the vast amount of empirical and theoretical research relevant to the issues discussed. Our goal is simply to cite representative examples of particularly relevant findings. Other papers in this *Frontiers* research topic review evidence showing that schizophrenia and related disorders involve impairments in various aspects of visual perception. This paper outlines hypotheses relating them to widely distributed mechanisms for context-sensitive gain-control, and, through that, to the better-known symptoms of schizophrenia. The perspective taken here overlaps in various ways and to various extents with several other theories. We do not claim priority for any of its components. One previous theory that we should relate it to, however, is our own. The central hypotheses examined here are similar to those that we proposed ten years ago (Phillips and Silverstein, 2003), except that we now emphasize a greater variety of possible functions and mechanisms. Then we emphasized contextual disambiguation, now we emphasize various other possible functions. Then we emphasized NMDARs as the mechanism for gain-control. Now we emphasize several other possibilities, including other intra-cellular mechanisms and various classes of inhibitory interneuron.

2. The organized complexity of mental life depends on context-sensitive gain-control

Many forms of organized complexity have arisen during nature's long journey from uniformity to maximal disorganization. Despite the ever-present forces of noise and disorder, biological systems have created many forms of dynamically organized adaptive complexity in open, holistic, far-from-

equilibrium, 'non-linear' systems with feedback. This has enabled them to evolve into many highly diverse forms of life whose activities are difficult and often impossible to predict with accuracy. As Isaac Newton is reputed to have said, the motion of stars can be predicted but not the madness of men. Nevertheless, all biological systems depend on prediction, and thus upon information about their world and themselves. This is needed for inference about distal things from proximal signals and about the likely consequences of possible activities. Though usually implicit, inference is central to biological systems because successful adaptation depends upon information about the conditions to which they are adapted. These inferences must be conditional on the current context because of the high-dimensionality of the world to which organisms must adapt; they must be probabilistic because of the endless variety of individual circumstances, the prevalence of deterministic chaos, and the subtleties of social interaction.

The centrality of unconscious inference to mental life was emphasized by Helmholtz in relation to perception more than a hundred years ago. This perspective has now produced many vigorously growing theories of cognition and brain function that are often referred to collectively as the 'Bayesian brain' (e.g. Feldman, 2001; Purves et al., 2001; Körding and Wolpert, 2004; Yuille and Kersten, 2006; Friston and Stephan, 2007; Friston 2010; Brown and Friston, 2012). So many empirical studies and theories have arisen from this perspective that there is no possibility of reviewing them here. Fortunately, they are also so prominent that we do not need to. All we need to do is to note that they usually imply a central role for context-sensitive gain-control, and then add a few caveats. Within theories of the hierarchical Bayesian brain, predictions are usually assumed to be transmitted from higher to lower levels of the hierarchy. Their function there is to control the gain of feed-forward transmission so that the inferences and predictions can be confirmed or improved. However, while predictions are sometimes assumed to arise only from higher levels in the hierarchy this assumption is not valid; predictions can also arise from concurrent streams within the same level. Various plausible neuronal mechanisms for gain-control have been proposed at both cellular and circuit levels, as discussed below. Many psychophysical, neurobiological, and computational studies support this Bayesian perspective (Clark, 2013); often by showing the effects of natural scene statistics in determining what is perceived. Though we have reservations about several aspects of these Bayesian theories, as clarified below, we do strongly agree with their emphasis on probabilistic inference, and we emphasize the dependence of inferential abilities on context-sensitive gain-control.

Our commitment to the view that context-sensitive gain-control operates in the service of probabilistic inference is subject to several important caveats, however. First, use of these notions in theoretical psychology and neuroscience requires a much broader foundation than can be provided solely by what is known as 'Bayes theorem'. That alone provides far too narrow a base. However, adequately broad logical foundations have been laid for theories of probabilistic inference by the American statistical physicist Edwin T. Jaynes (2003). Building on prior work of the mathematician Laplace and the statistician Jeffreys, Jaynes established the logical foundations of probability theory and inductive inference on the central assumption that probabilities are essentially epistemic; that is they quantify knowledge and uncertainty. Probabilities as relative frequencies are simply a special case. Application of that logic to theoretical neuroscience therefore requires uncertainty to be defined at the cellular or local circuit level. The many riches in Jaynes's analysis have been ignored by most neuroscientists and psychologists, but one notable exception is the neurophysiologist Fiorillo (2012) who sees the implications of his logic as requiring radical changes in the current consensus concerning the 'Bayesian brain'. We agree. The relevance of Jaynes's work to our perspective has therefore been examined in depth elsewhere (Phillips, 2012).

Our second caveat arises from Jaynes's analysis of the logical requirements for optimal Bayesian inference. He shows that optimal inference within a 'Bayesian' or epistemic conception of probability rests on a few desiderata that seem logically obvious, such as the necessity of using all of the relevant data available and not selecting only that supporting the hypothesis being tested.

Jaynes's desiderata are easy to meet when the exact problem to be solved is well-specified and the relevant data are clear and limited. That is rarely the case in relation to the systems-level inferences on which mental life depends, however. Even for the unconscious inferences of perception the desiderata can rarely, if ever, be fully met. For example, between what options must higher cortical regions choose when perceiving things? What prior data are relevant? On what should likelihood be conditioned? These are not questions to which we expect optimal answers, even though, given answers to them, the principles of epistemic inference are the optimal way to draw inferences from them.

Our third caveat concerns the relations between context, gain-control, and Bayesian priors. It may seem intuitively obvious that context is whatever provides the information on which priors are based. That is what most proponents of the Bayesian brain hypothesis assume, but that intuition is false if context controls gain as we and most others assume. Jaynes shows explicitly that priors do not have a secondary or dependent status in relation to the data being used to compute a new posterior probability. The essential equivalence of priors and likelihoods should be obvious given that posteriors are proportional to their product. Priors specify the probability of some hypothesis in any way that is logically independent of the data being used to compute a new posterior. Their effects can be either weaker or stronger than those of the current data. They can be based upon anything relevant, but they cannot control gain. That is because the effects of gain-control are logically dependent on the signal to be modulated, not logically independent. This does not mean that context cannot control gain; simply that it operates via the likelihoods, and not via the prior probability, as shown formally by Kay and Phillips (2010).

A further caveat can be briefly stated. We are not convinced that the common currency of feed-forward signals between cortical regions is prediction errors rather than the inferences used to make predictions as proposed by Rao and Ballard (1999). Proponents of that view often note apologetically that there is little or no neurobiological evidence for such an assumption as discussed by Clark (2013) and associated commentaries. We agree, and add that as time goes by this evidence gets even less. Fortunately, this is not a great problem for theories that emphasize predictive processing. All they need to do is to acknowledge that feed-forward transmission between regions predominantly signals the current state as inferred by the transmitting level (Spratling, 2008, 2009). This is fully compatible with amplification of both attended signals and feed-forward sensory signals that contradict strong within-level or feedback predictions.

Our final caveat concerns the architecture of information flow. Hierarchical Bayesian theories emphasize interactions between feed-forward and feed-back signals. Those theories do not deny that the number of concurrent channels within levels is far greater than the number of hierarchical levels, but they do ignore the necessity of using predictive relations between channels to maximise the coherence of inferences or decisions across channels. Maximizing coherence within as well as between levels is central to the perspective taken here.

We previously argued that the flexible adaptation of coherently organized percepts, thoughts, and actions to current circumstances depends upon cognitive coordination, and that this can be achieved by context-sensitive gain-control (Phillips and Silverstein, 2003). Those broad claims have been rigorously formalized using information theoretic concepts of conditional mutual information (e.g. Kay, Floreano, and Phillips, 1998; Kay and Phillips, 2010). Our claim that these concepts are useful to theoretical neuroscience and psychology is founded on cognitive, neurobiological, and clinical evidence, including that from visual psychophysics. The ubiquity of local ambiguity in visual perception and its resolution by context is well-established by many reviews of neurobiological and psychophysical studies (e.g. Phillips and Singer, 1997; Phillips and Silverstein, 2003; Butler et al., 2008; von der Malsburg, et al., 2010). This applies to the early stages of visual processing as discussed in detail below, and also to the higher levels of perceptual interpretation, such as in the dependence of object recognition on scene context (Bar, 2004). Taking these well-established findings as a given, the perspective outlined here formalizes conceptions of contextual

modulation rigorously in terms of computations that neural systems can perform, and relates them to detailed neurobiological mechanisms at both intra-cellular and local-circuit levels. These computations are described in abstract terms to show that they could be central to mental life in general. Thus, we see context-sensitive gain-control as operating in the service of the probabilistic inferences that are necessary to mental life. It is needed to ensure that the multiple concurrent inferences that are made moment-by-moment are both coherently related to each other and adaptively related to the current circumstances.

Several prominent theorists have previously argued that gain modulation is a major computational principle underlying brain function (e.g. Salinas and Thier; 2000; Salinas and Sejnowski, 2001, Chance et al., 2002), and some of its many computational uses will be listed Section 4. Within computational neuroscience gain modulation, or gain-control, is usually defined as a non-linear change in the response amplitude of a neuron that does not change its receptive field selectivity, i.e. its tuning function. Mathematically this has general utility because a population of responses to any receptive field variable, x, modulated by any context, y provides a basis set from which any function of x and y can be computed, and in many relevant cases it can be computed simply as a linear weighted sum (Salinas and Thier, 2000; Salinas and Sejnowski, 2001). Salinas and Thier (2000) note that to some researchers it can seem difficult to draw the line between selectivity and modulation, however, and that would greatly weaken any theory using it as a fundamental distinction. Fortunately, the distinction is clear to others, such as Lamme (2004) whose extensive electrophysiological findings on contextual modulation led him to the conclusion that it bears no relation to the neuron's receptive field properties and is mediated by mechanisms far removed from those that shape and tune the local receptive field. Furthermore, the distinction can be rigorously formulated using information theoretic concepts (Smyth et al, 1996). Primary driving receptive field input is that determining the variables and values to which the neuron is selectively tuned, and about which it thus transmits information. Gain-control changes the rate at which the neuron's output increases with the strength of the driving inputs to which it is selectively tuned but without fundamentally changing that selectivity. Gain-control may affect the narrowness of the tuning function, however, so it could change the precision or confidence with which the neuron transmits information about that to which it is specifically tuned. Contextual inputs are then simply defined as those that control gain. No information is transmitted specifically about the context other than through its modulatory effects. Thus no information should be transmitted specifically about the context when the receptive field input alone drives output to ceiling or when receptive field drive is absent, because then there is no signal to modulate (Smyth et al., 1996). In short, selective driving inputs are both necessary and sufficient to produce an output signal; contextual inputs are neither necessary nor sufficient. Recent optogenetic evidence convincingly supports this conception of context-sensitive gain-control, as will be made clear in the following sections.

3. Context-sensitive gain-control is a basic principle of cortical computation

There is now plenty of evidence that context-sensitive gain-control occurs within the mammalian cortex. Gain modulation combining retinal and gaze signals multiplicatively was first observed in single-unit recordings in neurons of the parietal cortex of the macaque monkey. Computational studies then showed that it could in principle provide a basis for converting the position of stimuli relative to the retina into position relative to the head (Andersen et al., 1985). Since then several other coordinate transformations that could be based on similar forms of gain-control have been seen in other cortical areas (e.g. Galletti and Battaglini, 1989; Salinas and Sejnowski, 2001). Gestalt grouping and sensitivity to context also involve context-sensitive gain-control as shown by evidence from single units, multiple units, local-field potentials, intra-cortical potentials, and macroscopic neuroimaging (see reviews by Phillips and Singer, 1997; Phillips and Silverstein, 2003; Lamme; 2004; Schwartz, Hsu, and Dayan, 2007; Salinas, 2009; Lee and Sherman, 2010;

Feldman and Friston 2010; Von der M et al., 2010). In addition to all the electrophysiological evidence common anatomical features of the canonical cortical circuit also suggest that the control of gain is a general principle of cortical computation (Douglas and Martin, 2007, 2008).

Interpretation of these electrophysiological and anatomical findings has been strengthened by many computational studies of the role of context-sensitivity and gain-control in perceptual and higher cognitive functions. Examples include studies by Huang and Grossberg (2010) in learning and visual search, and many others reviewed by Schwartz et al. (2007) in relation to the perception of orientation. Context-sensitive gain-control is central to the computational model by which Schwartz et al. (2009) account for dynamic Gestalt grouping, the effects of context, and their dependence on natural scene statistics, all of which have been observed in visual cortex. Their model uses normalization in the form of divisive gain-control, and they argue that it is relevant to various levels of the visual system. There are no grounds for assuming that context-sensitive gain-control is of relevance only to vision, however, and evidence that it also applies to other modalities will be mentioned below. Furthermore, contextual disambiguation and the dynamic grouping of coherently related elements may be of even greater importance to higher cognitive functions, such as language, for example. Our working assumption is therefore that context-sensitive gain-control provides a common foundation for cortical computation in general.

Some of the most convincing evidence concerning context-sensitive gain-control is now being provided by investigations that combine transgenic and optogenetic techniques with electrophysiological methods. Using optogenetic techniques experimenters can switch cortical layer specific genetically specified types of cortical neuron on or off with millimetre and millisecond precision in awake behaving animals. Studies using these techniques provide new insights into both the functions and mechanisms of context-sensitive gain-control in the cortex, as outlined below. These findings are emphasized here because they both further establish context-sensitive gain-control as a fundamental capability and shed new light on the mechanisms by which it is achieved.

These mechanisms include inhibitory interneurons, of which there are several classes and subtypes, all with different properties and functions. One major class are those expressing parvalbumin, a low-weight protein involved in various physiological processes, including neuronal signalling. The cortical neurons expressing parvalbumin on which we focus here will be referred to as PV interneurons. They include basket cells and chandelier cells in the neocortex, and are usually fast-spiking local-circuit neurons with synapses on specific perisomatic parts of pyramidal cells. Experiments using transgenic mice and optogenetic techniques in combination with single-unit electrophysiology have show that under natural conditions they can amplify or suppress the gain of pyramidal cell activity (Atallah et al., 2012). These experiments show that in mouse primary visual cortex PV interneurons control the gain of the response of layer 2/3 pyramidal cells in an essentially simple way. Optogenetically suppressing PV interneuron activity increased layer 2/3 pyramidal cell activity multiplicatively by a factor of 1.2 and added a constant amount. Optogenetically activating PV interneurons decreased pyramidal cell activity divisively by a factor of 1.4 and subtracted a constant amount (Atallah, et al. 2012). Furthermore, Atallah et al. (2012) show that small changes in PV interneuron-mediated inhibition can lead to robust changes in the response of pyramidal cells to visual stimuli without having any major impact on the selectivity of their tuning. This provides direct support for theories proposing that cortical computation is founded on processes that control gain without fundamentally changing tuning selectivity (e.g. Kay et al., 1998; Kay and Phillips, 2010). These optogenetic findings demonstrate that PV-mediated inhibition can provide a major circuit component for controlling gain. In addition, PV interneurons play a major role in generating and coordinating gamma rhythms, which, as we will discuss further below, may play a major role in the coordination of cognitive activities, including Gestalt grouping.

Optogenetic techniques have also recently revealed that in both anaesthetized and awake behaving mice excitatory cells in layer six of the primary visual cortex have a crucial role in controlling the gain of visually evoked activity in pyramidal neurons of the higher layers in the

same column without essentially changing the orientations to which they are selectively tuned. This gain-control involves intra-columnar projections from layer six excitatory neurons to superficial layer cells via inhibitory interneurons and establishes layer six as a major mediator of cortical gain-control (Olsen et al., 2012). The interneurons mediating this inhibition have yet to be positively identified, but we assume that they include PV interneurons. As layer six cells receive convergent inputs from both lower and higher brain areas and control gain with local precision they are well-suited to controlling gain in a locally specific way using information from a variety of sources. A major task for the future will be to find-out what kinds of context-sensitivity are mediated by layer six pyramidal cells.

In addition to the PV-expressing class of inhibitory interneuron there is another large class, including Martinotti cells, which express the neuropeptide somatostatin (SOM interneurons). They are not fast-spiking and have axonal arbors on the distal dendrites of pyramidal cells. They are widely distributed across mammalian cortex, including that of humans, and are involved in the regulation of various processes. Of particular relevance here is their role in visual gain-control. It has recently been shown using optogenetic techniques that SOM interneurons contribute to surround suppression (Adesnik, et al., 2012). It was first shown that the main excitatory input to layer 2/3 SOMs are horizontal axons of layer 2/3, and that they prefer large to small stimuli. This enables them to contribute to surround suppression, which they were shown to do by selectively reducing SOM interneuron activity. This significantly reduced surround suppression of layer 2/3 neurons by between 10 and 30%. SOM interneurons are but one of several mechanisms for surround suppression, however, as it is also in part inherited from earlier stages of visual processing, and is also in part due to other types of inhibitory interneuron and circuit mechanisms (Adesnik et al., 2012). A plausible default assumption is that, as SOM-expressing interneurons are common across cortex as a whole, visual surround-suppression is but one example of a computational strategy with a much wider general utility (e.g., Series et al., 2003).

4. Context-sensitive gain-control has several compuational functions

Context-sensitive gain-control has several computational functions; each with wide generality. Though distinct, they all depend upon some form of context-sensitive gain-control. Here we simply list some of the most well known, making no attempt to review the substantial body of research available on each. Some of those listed may be seen as a particular form of a broader underlying function. For example, though distinct, surround suppression and attention may nevertheless be different forms of divisive normalization (Reynolds and Heeger, 2009). Furthermore, many, but not all, improve coding efficiency.

First, one obvious function of wide generality is contextual disambiguation, which could be achieved by multiplicatively increasing the gain on interpretations that are coherently related to the context and reducing the gain on those that are not. Examples of this include the enhancement of low-contrast edge detection by collinear flankers (Polat and Sagi, 1993), sensitivity of object recognition to scene context (Bar, 2004), word-sense disambiguation and many other examples reviewed by Phillips and Singer (1997) and by Phillips and Silverstein (2003). We assume that examples of contextual disambiguation include coordination of multiple distinct probabilistic decisions so that they form a coherent whole. Examples of this at the level of object perception level include the interpretation of ambiguous figures, such as the duck-rabbit figure. When perception switches between alternative interpretations it usually does so as a whole, suggesting that all the distinct decisions that this involves are coordinated by some form of context-sensitive gain-control that operates so as to maximize coherence over the whole figure that is being interpreted (Klemm et al., 2000).

Second, divisive normalization is a form of gain-control that has been described as a canonical computation because it has various uses from low levels of sensory processing to higher levels of

cognition such as value encoding (Carandini and Heeger, 2012). These include surround suppression (Simoncelli and Schwartz, 1999) which expands dynamic range by adapting the sensitivity of a population of neurons to current input levels while keeping the ratio of their outputs constant (Heeger, 1992), invariant object recognition (Kouh and Poggio, 2008), the reduction of redundancy (Schwartz and Simoncelli, 2001), and various other ways of producing efficient codes (Carandini and Heeger, 2012). The driving summation field in normalization theory is equivalent to the receptive field (RF) in coherent infomax theory (e.g. Phillips and Singer, 1997). The suppressive field specifying the denominator is one form of context-sensitive gain-control, i.e. it is part of the contextual field (CF) in coherent infomax theory. Recent neurophysiological findings show clearly one way in which input normalization by global feedforward inhibition can expand the dynamic range of cortical activities (Pouille et al., 2009). The coordinated action of direct excitation and feed-forward inhibition enables populations of pyramidal cells to remain sensitive to weak inputs, but not saturate in response to stronger inputs. Taking tilt-illusions as a concrete example, Schwartz et al (2007) provide a rigorous computational analysis of the way in which spatial and temporal contexts make a crucial contribution to perception via their effects on context-sensitive gain-control in general and divisive normalization in particular.

Third, coordinate transformation was one of the first uses of gain-control for which there was both empirical and theoretical evidence. It involves 'gain fields' that could in principle be used to compute the position of a target relative to the head given information about its position relative to the retina and of the position of the retina relative to the head (Anderson, et al., 1985). Since then a great deal of evidence has been obtained for the use of such gain-fields in several other forms of coordinate transformation (Salinas, 2009).

Fourth, dynamic Gestalt grouping may also be achieved by some form of context-sensitive gain-control. Grouping, sometimes referred to as 'integration', can be treated as a separate class of functions quite distinct from gain-control (e.g. Butler et al., 2008), but here we include it within a broad conception of gain-control for several reasons as noted above. Lamme (2004), who has long studied contextual modulation extensively, argues that perceptual grouping is one of its main functions. Furthermore, there is much evidence that gain-control on a fast time-scale so as to synchronize coherent subsets could provide a basis for many cognitive functions including Gestalt figural organization (von der Malsburg et al., 2010). Finally, as we will show below, dynamic Gestalt grouping depends upon some of the same mechanisms as other forms of context-sensitive gain-control.

Fifth, object and face recognition are highly context-sensitive because the probability of seeing any given object or face depends so heavily upon the context (Bar, 2004). Moreover, as we show below, disorders in which visual context processing is impaired are also associated with substantial abnormalities in face perception. Context-sensitive gain-control may also contribute to the invariance of object recognition because normalization can be used to compute outputs that are insensitive to irrelevant stimulus dimensions (Salinas, 2009).

Sixth, prima facie, selective attention seems to be concerned with enhancing selected signals, while suppressing irrelevant signals. Computational, psychophysical, and physiological evidence supports that intuition, and much of that evidence was accounted for by the biased-competition theory (Desimone and Duncan, 1995). That has now been developed into an even more comprehensive theory in which attention is viewed as a form of divisive normalization (Reynolds and Heeger (2009), and thus as a form of context-sensitive gain-control.

Seventh, context-sensitive gain-control can produce efficient codes by using predictions to suppress the feed-forward transmission of any data that is highly probable, and thus not informative. Predictions are often assumed to be computed using hierarchical Bayesian inference (e.g. Lee and Mumford, 2003), and that possibility has now been developed into several highly influential theories of the Bayesian brain as noted above. It may seem that these predictive coding theories are in conflict with the biased-competition theory of selective attention because they imply the

suppression of predicted data, rather than its enhancement. It has been shown computationally that predictive coding and biased-competition are compatible, however, and can be combined in a single model in which prediction-error processing occurs within rather than between cortical regions. Selective attention can then modulate those signals, so as to enhance, rather than suppress, the selected interpretations (Spratling, 2008, Spratling, et al. 2009). A recent development of that model has been used to argue that a distinction between driving and modulating inputs could arise as an emergent circuit-level property of the perceptual inference performed using divisive input modulation, thus enabling it to account for surround suppression, and contour integration, as well as predictive coding and selective attention (Spratling, submitted). Note, however, that arguments for the possibility of such a circuit-level mechanism for distinguishing between driving and modulatory inputs are not arguments against other possible mechanisms, for which there is plenty of evidence as reviewed in the following section.

Eighth, a neural network model has shown that contextual modulation can be used to select one of a number of possible arbitrary mappings from sensory stimuli to motor actions by controlling gain, thus helping to explain how higher organisms can rapidly and flexibly adapt their actions to current conditions (Salinas, 2004). Though that model is concerned with the selection of motor commands, the same computations could apply equally well to the selection of inner percepts and thoughts as assumed by the closely related theory of coherent infomax (Kay, Floreano, and Phillips, 1998; Kay and Phillips, 2010). Though these two theories were developed independently they use essentially the same mathematical function to specify how the gain of the response to driving inputs is modulated by context. Both theories are therefore strengthened by this convergence because each provides further grounds on which to support the other.

It may also be possible to relate context-sensitive gain-control to more subjective aspects of human conscious experience. One recent development suggesting how that might be done is a theory of interoceptive inference which offers a unified account of emotion, the sense of presence, and the sense of agency (Seth et al, 2011). By analogy with predictive coding theories of visual perception, interoceptive inference is hypothesized to involve a hierarchy of top-down predictions that guide the interpretation of bottom-up interoceptive signals. The subjective sense of the reality of the self and of the external world, referred to as conscious ‘presence’, is hypothesized to depend on the successful suppression of informative interoceptive signals by precise top-down predictions (Seth et al., 2011). Similarly, the subjective sense of agency is hypothesized to arise from precise predictions of the sensory consequences of actions, as proposed by Fletcher and Frith (2009). The theory of Seth et al (2011) synthesizes much of the relevant phenomenology, neurobiology, and psychopathology, and the precision of prediction error signals plays a key role in their theory. This is optimized by using context to control the gain of prediction error units. They emphasize the role of the classic neuromodulators in doing this, and dopamine in particular, but more locally-specific coordinating interactions must also play a role. Their theory is relevant here because it depends on the modulation of precision by gain-control, and because it explicitly shows how impaired gain-control in the form of reduced precision could produce positive symptoms of psychosis, as discussed in Section 6.3. Though Seth et al. (2011) emphasize feed-forward transmission of prediction-errors, rather than of the inferences used to make predictions, we do not think that essential to theories of predictive inference as explained above.

5. There are various local-circuit and cellular mechanisms for context-sensitive gain-control

As clearly shown by previous reviews there are various ways in which gain can be modulated by context within the cortex (e.g. Salinas, 2009; Silver, 2010). There is no simple one-to-one mapping between these mechanisms and the various functions of gain-control discussed above because one mechanism may contribute to more than one function, and one function may be performed by more than one mechanism. Different mechanisms are suited to different roles, however. For example, as

noted above, SOM interneurons play a major role in surround-suppression (Adesnik et al., 2012), whereas PV interneurons may contribute to Gestalt grouping via the generation and synchronization of gamma rhythms (Gonzaloz-burgos, et al. 2010), in addition to amplifying or suppressing activity (Atallah et al., 2012) using information from a wide variety of sources.

The simplest way in which pyramidal cells could increase the gain of other pyramidal cells so as to amplify coherent activities is via direct connections between them. It is likely that such a mechanism is used because it is the fastest and most energy efficient. In addition, it requires the transmission of a great deal of information and about 75% of all cortical connections are between pyramidal cells (Braitenberg and Schuz, 1991). Furthermore, NMDARs, which provide a means by which such connections can control gain (Phillips and Silverstein, 2003), are highly expressed on pyramidal cells. Finally, recurrent excitation between pyramidal cells that is mediated by NMDARs may also underlie sustained neuronal firing, which is a potential neural substrate for working memory (Gonzalez-Burgos and Lewis, 2008). Direct NMDAR-mediated interactions between pyramidal cells are therefore likely to be a widely used mechanism for controlling gain so as to amplify coherently related activities.

Recurrent connections between pyramidal cells require tight inhibitory control to prevent runaway excitation, however. That is in part provided by PV interneurons which, by targeting the perisomatic membrane compartment of pyramidal cells, exert powerful control of spike initiation. Much is now known about the role of inhibition in shaping cortical activity (Isaacson and Scanziani, 2010), and it plays a major role in several of the gain-control mechanisms to be outlined next.

Silver (2010) reviewed a wealth of intra-cellular mechanisms by which gain-control can be implemented. These include shunting inhibition, background noise induced by balanced excitatory and inhibitory background input, nonlinear dendritic integration such as dendritically localized NMDAR-mediated spikes, and short-term depression (STD) which can provide a mechanism for multiplicative gain-control if the contextual inputs are received on synapses distant from the cell body (Silver, 2010). Two mechanisms may be of particular relevance to issues considered here. One involves the PV interneurons whose ability to amplify or suppress pyramidal cell activity was outlined in the previous section. They are also known to modulate temporal precision and also to generate and synchronize gamma and other high-frequency rhythms. They do this by controlling the ‘window-of-opportunity’ within which pyramidal cells can generate spikes given their driving inputs (Gonzalez-Burgos and Lewis, 2008; Phillips et al., 2010). Computational modelling shows that by synchronizing the local activity of PV interneurons to a greater or lesser degree this window can be opened more or less. This is because PV neurons exert a powerful veto on spiking, so synchronizing their bursts also synchronizes the periods between bursts. This synchronized disinhibition therefore provides a ‘window of opportunity’ for spiking that could provide a means by which contextual inputs, such as those from selective attention, could control the gain of pyramidal cell responses to their driving inputs (Tiesinga et al., 2008). We therefore need to know more about the sources of input to PV interneurons. It is known that in rodent primary somatosensory cortex their excitatory inputs are on distal dendrites, and come from both thalamic and intracortical sources, whereas their inhibitory inputs are somatic and perisomatic (Kameda et al., 2012), but we need to know far more about those sources.

The other mechanism that may be of particular relevance is modulation of proximally driven activity by distal nonlinear dendritic currents that can either increase or decrease response gain at the soma (Silver, 2010). The possibility that distal dendritic tuft inputs might modulate response gain to inputs at the soma and basal dendrites was explored computationally by Körding and König (2000). They showed that this enables the learning and processing of information that is relevant to the context. Lee and Sherman (2010) distinguished two classes of glutamatergic pathways in the auditory cortex, termed “drivers” and “modulators”. Driving inputs are the information-bearing pathways, while modulators regulate transmission of the driving information. Driving inputs are received by proximal dendrites, whereas modulatory inputs are received by distal dendrites. Lee and

Sherman (2010) also note that these two glutamatergic pathways are fundamentally different in other ways. Driving inputs are received from thick axons at ionotropic synapses, and produce large EPSPs via depressing synapses and dense synaptic arbors. Modulatory inputs are received from thin axons at ionotropic and metabotropic synapses, and they produce small EPSPs via facilitating synapses and sparse synaptic arbors. All these differences are in agreement with the distinction between driving inputs and context-sensitive gain-control on which our hypotheses here are based. Lee and Sherman (2010) argue that their distinction between drivers and modulators clarifies the function of the many parallel and descending pathways in the auditory and other sensory pathways. We agree, and argue for the potential relevance of such a distinction to cortical processing in general. Further support for the view that some contextual influences operate via thin distal dendrites is that the cortico-cortical projections that are likely to convey them terminate preferentially in superficial cortical layers and on the distal segments of apical dendrites of pyramidal cells, which are especially rich in NMDARs (Monaghan and Cotman, 1985; Rosier et al., 1993). We do not suggest that all contextual influences operate via distal dendrites, however. Inhibitory modulatory influences from PV cells are received on or proximal to the soma, so they do not operate via distal synapses. Furthermore, other mechanisms that are both modulatory and proximal may remain to be discovered. A simple summary of the current evidence is that direct modulatory interactions between pyramidal cells seem to be predominantly distal, as does modulation by inhibitory SOM interneurons, whereas modulation by inhibitory PV interneurons is proximal to or on the soma.

Though much remains to be learned about the functions and mechanisms of context-sensitive gain-control, one important conclusion is already clear. It is not a single function with a single mechanism. It is a family of regulatory functions served by a variety of mechanisms. The possible mechanisms sketched above do not all operate independently, however, as there are multiple interactions between them. For example, the inhibitory interneuron activity that produces changes in pyramidal cell gain is in some conditions itself modulated by NMDAR-mediated input to the inhibitory interneurons. Thus pyramidal cells modulate each others' activities directly via NMDAR-mediated connections between them, and indirectly via their effects on the modulation produced by inhibitory interneuron activity. The different mechanisms nevertheless make different contributions as they are suited to different conditions. It is going to be difficult to find out exactly which mechanisms do what because their capabilities depend on so many things (Silver, 2010). These include: 1) whether it is input or output gain that is modulated; 2) the morphological complexity of the cell whose activity is modulated; 3) whether the modulatory inputs are proximal to the soma or on distal apical dendrites; 4) whether the modulatory synapses are clustered or widely distributed; 5) whether the gain is to be increased multiplicatively or decreased divisively; 6) the time-scale over which gain is modulated; and 7) whether it operates on sustained high-frequency rate signals or on sparse and brief but temporally correlated population signals. A major task for cognitive neuroscience is therefore to find out which of the various mechanisms for context-sensitive gain-control contribute to each of its various uses. This will not be an easy task, but disorders in which both the functions and the mechanisms of context-sensitive gain-control are impaired, such as schizophrenia, may be of help.

6. The functions and mechanisms of context-sensitive gain-control are impaired in schizophrenia

Here we discuss visual and other impairments in schizophrenia in the light of the functions and mechanisms of context-sensitive gain-control reviewed above. It will not be easy to distinguish primary from secondary impairments because there are so many interdependencies between the different mechanisms, but that is not crucial to our current goals. Furthermore, as our focus is on impairments of basic capabilities common to many different cognitive domains and cortical regions,

we are not constrained to considering only impairments that are specific to perception. We do need to ask whether they are specific to context-sensitive gain-control or not, however. The evidence suggests that schizophrenia-related impairments are rarely all-or-none, so our default working assumption is that the capabilities impaired are still operating to some extent, though less effectively. A demonstration that some relevant capability is still present to some extent in patients tells us little. What we need to know is whether it is impaired or not, and, if so, how and on what that depends.

6.1. Impairments of visual perception in schizophrenia involve context-sensitive gain-control

It is now well established that there are impairments of visual perception in schizophrenia, and that they involve context-sensitivity and gain-control. There is no need for a comprehensive review of these impairments here because they will be the central focus of other papers within this *Frontiers* Research Topic. Here it will suffice to comment on the overview of visual disorders in schizophrenia arising from the NIMH-sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) meeting organized to assess this issue (Butler, et al, 2008, 2012; Green et al.,), and to outline a few other relevant findings.

Butler et al (2008) divided the visual functions that are impaired in schizophrenic disorders into two groups, ‘gain control’ and ‘integration’. They defined gain control as processes optimizing response to stimuli within a particular surrounding context. One form of this is that in which the neurons’ dynamic range is modulated so as to increase responses to differences between adjacent and successive stimuli, as seen, for example, in ‘pop-out’ and ‘surround suppression’ paradigms. Divisive gain normalization is the appropriate form of gain-control in that case, and center-surround suppression has been shown to be reduced in schizophrenia (Dakin et al., 2005; Yoon et al., 2009). Another form of gain control (Butler et al., 2008) is the amplification of driving inputs that are present but weak such as those produced by near-threshold stimuli, as shown, for example, by facilitation of the detection of a low-contrast edge by collinear flankers. This form of gain-control can be studied in various psychophysical and electrophysiological paradigms that measure contrast-sensitivity under conditions designed to reveal the operation of either the magnocellular or parvocellular visual pathway, and with either transient, moving, or steady-state stimulation. In general these paradigms include any in which the preceding, concurrent, or following context amplifies signals coherently related to that context. Multiplicative gain amplification is appropriate for this form of gain-control. It is clearly impaired in schizophrenia but not in other forms of serious mental illness (Butler et al. 2005; Keri et al, 2005a, 2005b, 2009). There is good evidence that impairment may be greater in magnocellular than in parvocellular pathways (Butler et al., 2005; Butler et al., 2008).

Butler et al (2008) define ‘integration’ as the process linking the output of neurons into globally coherent sub-subsets, where their individual activities are assumed to code for local attributes. This is therefore equivalent to what is here and elsewhere referred to as dynamic Gestalt grouping. There are many paradigms for studying such grouping, with contour integration being an example that is often used because it can be rigorously controlled. Since 1961 (Snyder, 1961; Snyder et al., 1961), many of these paradigms have been used to study visual grouping in schizophrenia, with the general conclusion being that it is impaired, as reviewed by Silverstein and Keane (2011). Impaired grouping in schizophrenia has been demonstrated in studies of perceptual organization of static forms, fragmented forms, completion of occluded objects, illusory correlations, and coherent motion, and this evidence includes psychophysical, electrophysiological, and brain imaging data (e.g. Spencer, et al., 2003; Silverstein, et al., 2009; Chen, 2011; Sehatpour et al., 2011).

It is well-established that face processing is impaired in schizophrenia (e.g. Uhlhaas et al., 2006a; Turetsky et al., 2007; Silverstein et al., 2010; Soria Bauser et al., 2012), but as perceptual deficits are not confined to higher levels of processing, deficits at lower levels may account for a significant portion of the face processing impairments (Turetsky et al. 2007; Silverstein et al 2010).

Impairments in face perception are also observed in body dysmorphic disorder, the only other psychiatric condition in which perceptual organization impairments have been observed (Feusner et al., 2007, 2010), and where half of the patient population also exhibits delusional psychotic symptoms (Phillips et al., 2006).

Schizophrenia-related deficits have been shown to be specific to context-sensitive gain-control in experiments that use conditions in which context is misleading. If performance deficits are specifically due to reduced effects of context then performance could be supra-normal when context is misleading. This was shown to be the case in a size perception task where surrounding figures provided a context that was helpful in some conditions and misleading in others (Uhlhaas et al., 2006b, Silverstein et al., 1996). Patients were neither helped by helpful context nor hindered by misleading context. Similar results were reported by Dakin et al (2005) who found that schizophrenia patients had decreased center-surround antagonism in a contrast perception task. High-contrast surrounds reduced perceived contrast in control subjects but not for most of the patients, with the consequence that patient's judgements were then more veridical than normal. Finally, Tadin et al (2006) found that schizophrenia patients had reduced surround suppression in a motion perception paradigm, including more veridical performance in conditions where context was misleading.

Figure-ground segregation using brief temporal cues is also severely impaired in many but not all schizophrenia patients (Hancock et al., 2008). This was demonstrated in a task based on figure-ground segregation by onset-asynchrony. Performance in this task is likely to be particularly sensitive to the function of magnocellular pathways because it is concerned with rapid attentional capture, at low spatial resolution, of overall stimulus organisation. Most people can segregate figure from ground when the asynchrony of their onsets is about 24 msec, but 7 of 9 chronically disorganized schizophrenia patients required asynchronies of at least 50 to 100 msec. (Hancock et al, 2008). Furthermore, 7 of 63 undergraduate students also showed poor temporal resolution in this task, four of whom had schizotypy disorganisation scores well into the clinical range, suggesting that this psychophysical paradigm may provide a useful endophentoype for the disorder.

Eight possible uses for context-sensitive gain-control were listed above. So far we have cited evidence that four are impaired in schizophrenia. What of the other four, i.e. selective attention, modulation of precision in probabilistic inference, arbitrary input-output mappings, and coordinate transformation? All are relevant to vision, though none to vision alone. Selective attention is clearly one of the major impairments in schizophrenia, and is related to positive symptoms (Cornblatt et al., 1985). Imprecise signalling in probabilistic inference may also make a major contribution to the positive symptoms (e.g. Fletcher and Frith, 2009; Seth et al, 2011) as will be discussed further below. The use of context to guide selection of one from a number of possible mappings is also likely to be impaired, though we know of no work explicitly relating that to the model of Salinas (2004). Finally, although it is often emphasized as a foremost function of gain-control (Salinas and Thier 2000, Salinas, 2009), coordinate transformation seems the least likely to be impaired in schizophrenia. Schizophrenia patients show no obvious signs of disordered gaze or reaching, or other impairments indicative of inadequate coordinate transformation. Schizophrenia patients do demonstrate heightened spatial frame illusions, and this may suggest abnormalities in visuo-motor functioning (Chen et al., 2011). Moreover, schizophrenia patients do not demonstrate the normal degree of attenuation of sensory feedback during self-initiated movements, and this has been proposed as a factor in the formation of delusions of control by external entities (Landgraf, et al., 2012). Similarly, schizophrenia patients show heightened susceptibility to the rubber hand illusion, suggesting a more dynamic and flexible representation of their body in space (Thakkar et al., 2011). None of these findings suggest any direct impairments of coordinate transformation, however. Maybe there are none. The obvious prediction from our theory is that they will be impaired to the extent that they depend upon the same neuronal mechanisms for context-sensitive gain-control as its other uses. One important possibility is that, if coordinate transformation does use some form of

gain-control, it is not a form that is sensitive to context in a way comparable to the other forms emphasized here and which are impaired in schizophrenia. In short, this suggests that it is not gain-control in general that is impaired in schizophrenia, but only context-sensitive gain-control, as we have assumed throughout.

Thus, psychophysical studies have shown that the context-sensitive perceptual operations of divisive gain suppression, multiplicative gain amplification, dynamic Gestalt grouping, and face and object recognition are all impaired in schizophrenic disorders, though to different extents in different cases and conditions. This evidence shows that such impairments can occur at multiple levels of all or most sub-modalities of visual processing, and suggests that they probably also occur at multiple levels in other modalities. These impairments are not constant over time, however. Some have been demonstrated to be state-sensitive in that they are more pronounced when patients are acutely psychotic compared to when their symptoms are in remission (Keane et al., in press; Silverstein and Keane, 2009; Silverstein et al., submitted, this research topic; Uhlhaas et al 2005). Moreover, some of these state-sensitive impairments also occur in healthy volunteers administered ketamine, an NMDA antagonist (Uhlhaas et al, 2007; Morgan et al., 2011), as expected given the neuropathophysiological evidence discussed in the following sub-section.

6.2. Neuronal mechanisms for context-sensitive gain-control are impaired in schizophrenia

The classical neuromodulators that have long been implicated in schizophrenia, such as dopamine and acetylcholine, provide an obvious form of gain-control. Their effects are slow and diffuse, however, whereas the cognitive interactions that are most obviously impaired in schizophrenia must have high temporo-spatial specificity because they convey detailed cognitive content. Modulatory interactions within and between the glutamatergic and GABAergic systems that convey that content must therefore also be involved. Our focus here is therefore on possible impairments of the modulatory interactions that occur within those systems, which are themselves modulated by the classical neuromodulators.

Some modulatory interactions within the glutamatergic system are produced via direct NMDAR-mediated interactions between pyramidal cells, as outlined in Section 5. There is ample evidence that NMDAR-mediated signalling is impaired in schizophrenia as reviewed many times elsewhere (e.g. Phillips and Silverstein, 2003; Loh et al, 2007; Corlett et al, 2010; Kantrowitz and Javitt, 2010; Moghaddam and Javitt, 2012). Furthermore, a review of the evidence on genetic susceptibility and gene expression concluded that, although there are probably direct and indirect links to both dopaminergic and GABAergic signalling, glutamate transmission via NMDARs is especially implicated (Harrison and Weinberger, 2005). Conclusive evidence that NMDAR hypofunction can produce many schizophrenic symptoms comes from an autoimmune disease first reported in 2007. This is an anti-NMDAR encephalitis that progressively reduces the activity of NMDARs by capping and internalizing them (Hughes et al., 2010). Patients present with acute schizophrenia-like symptoms, including paranoia. They are often admitted to psychiatric institutions and later develop severe catatonia, catalepsy, and stereotyped movement disorders. Given the unequivocal evidence that NMDAR hypofunction can produce symptoms of schizophrenia, and that those receptors are most dense on pyramidal cells, our working hypothesis is that impaired NMDAR-mediated interactions between pyramidal cells are a substantial part of the pathophysiology of schizophrenia. That could contribute to deficits in several of the uses for context-sensitive gain-control, as listed above, including contextual disambiguation and Gestalt grouping.

Though less dense than on pyramidal cells, there are also NMDARs on the inhibitory interneurons on which several of the other mechanisms for context-sensitive gain-control discussed above depend. There is plenty of evidence that their activity is also impaired in schizophrenia. Multiple studies have reported alterations in markers of inhibitory GABAergic neuronal activity (e.g. Lewis, et al., 2005; Gonzalez-Burgos et al., 2010; Lewis, 2012), including their association with reduced center-surround suppression in visual cortex (Yoon et al., 2010). This deficit appears

to be particularly pronounced in the subset of GABAergic neurons that express the calcium-binding protein parvalbumin (PV) (Hashimoto et al., 2003). Thus, this provides another route by which NMDAR hypofunction could contribute to some of the deficits in schizophrenia. For example, when transgenic mice are generated in which NMDARs are selectively deleted from cortical and hippocampal GABAergic PV interneurons this produces selective molecular, physiological, and behavioural changes similar to some of those in schizophrenia (Nakasawa et al. 2012). Behrens and Sejnowski (2009) review evidence suggesting how dysregulation of PV interneurons in the developing cortex could explain the late onset of schizophrenic symptoms as well as the differences between the effects of brief and prolonged exposure to NMDA antagonists (Jentsch and Roth, 1999). The division of PV interneurons into two major classes is based on the principal target of their axon terminals. The axon terminals of the basket cell class target the cell body of pyramidal neurons and their proximal dendrites. The other major class, chandelier cells, gives rise to terminals that exclusively target the axon initial segments of pyramidal cells. There is evidence that both classes are impaired in a way that is specific to schizophrenia (Lewis et al. 2005; Lewis 2012). PV interneurons also play a major role in setting the levels of temporal precision. This suggests that their impairments may play a major role in the reduced temporal precision of figure-ground segregation in schizophrenia reported by Hancock et al. (2008) and summarized above. Further evidence for the role of PV interneurons and synchronized rhythms in the development of schizophrenia is provided by Lee et al (2013) who reported that, in a neurodevelopmental rat model of schizophrenia, adolescent cognitive training reduced PV-labelling in mature prefrontal interneurons, normalized the synchrony of neural oscillations between the left and right hippocampi, and prevented adult cognitive impairment.

Impairments of inhibitory interneuron activity could thus have several cognitive consequences. Many researchers, such as Lewis (2012), focus on consequences for working memory (WM) and executive functions of the dorsolateral prefrontal cortex. We agree that dysfunctions of PV interneurons have consequences for WM and executive function, but from our perspective that provides far too narrow a focus as argued above. There is no good evidence linking the many selective impairments of perception reviewed here and elsewhere to WM or executive impairments. Effects of PV GABAergic impairment could also include many other cognitive functions as a consequence of their pivotal role in temporally precise activities including the generation and timing of rhythmic activity in the gamma frequency range (Cobb et al, 1995; Pouille and Scanziani, 2001). It is well-established that a wide range of cognitive deficits are associated with NMDAR hypofunction and changed gamma-band activity in schizophrenia (Dzirasa et al., 2009; Uhlhaas and Singer; 2010). Uhlhaas and Singer (2012) now review more evidence showing that synchronization of high-frequency rhythms is essential for dynamic coordination of the cortical activity that it is impaired in schizophrenia and autistic spectrum disorders. They summarize evidence suggesting that impaired long-range dynamic coordination of activity across brain-regions may be central to these disorders. The effects of impaired NMDAR-mediated neurotransmission on pyramidal cells and PV interneurons are particularly implicated. For example, the correlation between reduced GABAergic tone and reduced surround suppression in schizophrenia (Yoon et al., 2010) is probably mediated by gamma frequency oscillations, as recent research indicates a strong relationship between these three phenomena in healthy humans (Edden et al., 2009). Studies of rhythmic activities, their local and long-range coordination, developmental trajectories, and pathologies have thus revealed much, and we expect them to reveal even more in future. From the point-of-view being developed the phenomena that they observe offer a wide window on processes of context-sensitive gain-control. The objective of those processes extends far beyond the generation of rhythmic activities, however. Their fundamental objective is to guide the many highly distributed probabilistic inferences that must be made at each moment toward decisions that are both coherent and well-adapted to current circumstances.

In addition to PV interneurons, other classes of inhibitory interneuron also contribute to context-sensitive gain-control. Evidence that somatostatin expressing interneurons (SOM interneurons), such as Martinotti cells, play a major role in surround suppression (Adesnik, et al., 2012) was cited above. There is evidence for SOM interneuron impairment in schizophrenia (Morris, et al., 2008), and surround suppression is one of the forms of context-sensitive gain-control shown to be impaired in schizophrenia. Therefore, that impairment may be due to impairments of SOM interneuron activity, though not necessarily so because other mechanisms also contribute to surround suppression.

Overall, the neurobiological evidence suggests that schizophrenia involves impairments of NMDAR-mediated transmission and of the activities of PV and SOM inhibitory interneurons. All play a major role in context-sensitive gain-control, as outlined in Section 5. An important direction for future research is to characterize the degree to which these physiological impairments map onto the emergence and remission of the cognitive and symptom features of schizophrenia to which we and others hypothesize they are related. As noted above, there is growing evidence for: 1) state-sensitivity of impairments in context-sensitive gain-control in schizophrenia (Silverstein et al., submitted; Keane et al, in press; Uhlhaas et al., 2005, Silverstein et al., 1996; Silverstein and Keane, 2009); 2) relationships between reduced contextual effects in perception and fragmentation in thinking (Horton and Silverstein, 2011; Silverstein and Keane, 2011; Uhlhaas et al., 2006); and 3) relationships between abnormal GABAergic activity and context-sensitive gain-control in schizophrenia (Yoon et al., 2010). Symptoms are, by definition, state related, and many theories now relate positive and disorganized symptoms of psychosis to altered states of NMDARs and interneuron activity. However, the development of pharmacotherapy on the basis of these theories, though promising, has not yet clearly improved on clozapine, which has been available for 50 years (Barch, 2010; Moghaddam and Javitt, 2012). This may, in part, be due to the difficulty of specifying clinically optimal doses. It could also be related to the need to distinguish between subtypes of receptor and post-synaptic cell. If impairments are due to reduced activity of only a particular NMDAR subtype on a particular class of post-synaptic cell, for example, then they would not be overcome by a systemic enhancement of NMDAR activity in general. The functional role and developmental trajectory of specific NMDAR subunits therefore needs to be better understood.

6.3. The positive symptoms of schizophrenia can be related to context-sensitive inference and gain-control

Psychiatrists have often concluded that contextual regulation of ongoing processing is particularly relevant to the induction of thought disorder (e.g. Barrera et al, 2005). Over the last few years this possibility has been developed into rigorously formulated theories that focus on the use of context to guide probabilistic inference toward inferences that are both coherently related to each other and well adapted to the current circumstances. These theories assume a form of hierarchical Bayesian inference that adapts and learns by reducing prediction error, where the predictions arise from higher levels of processing (e.g. Friston, 2010), and perhaps also by lateral interactions within levels. Such theories have been used to explain hallucinations (e.g. Friston, 2005) and various forms of delusion (e.g. Hemsley and Garrety, 1985; Corlett et al., 2007; Fletcher and Frith, 2009; Clark, 2013). In essence, to the extent that perception is under-constrained by prior experience of statistical regularities in the world, misperceptions and false attributions of meanings can result. These can produce a sense that the world is changing, giving rise to delusional explanations for these subjective changes. Delusions of agency are also well-explained by these models on the assumption that they arise from reduced precision in the predictions of self-induced sensory signals (Fletcher and Frith, 2009; Stephan et al., 2009; Synofzyk, 2010). In Section 4 we cited work showing how theories of this kind can explain conscious presence as arising from the correct prediction of interoceptive signals (Seth et al (2011). That theory explains how disorders of both conscious presence and emotion could arise from reductions in the context-sensitivity and precision

of probabilistic inference. Such theories can explain many of the psychotic symptoms that are seen in schizophrenia patients. Thus, they may provide important insights into the well-established symptoms of schizophrenia, and all depend upon context-sensitive gain-control. They imply a distinction between drivers and modulators because the predictions that are central to these accounts are thought to be modulatory and implemented by specialized synaptic interactions, such as those using NMDARs and inhibitory interneurons. Though we are not convinced by some aspects of theories based on predictive coding (Silverstein, 2013; Phillips 2013), we agree with their emphasis upon the necessity of using probabilistic inference to interpret interoceptive inputs as well as those from the external world, and with an emphasis upon the role of context-sensitive gain-control in doing that. Many of the positive symptoms of schizophrenia can thus be seen as arising from predictions that are pathologically imprecise because inadequate use is made of context to make them more precise. The use of contextual modulation can also enable the selection of perceptual interpretations or motor commands that have low probability overall, but high probability in special contexts. Thus, in addition to the symptoms noted above, weakened context-sensitivity could also lead to various other impairments of perception, thought, and action. Recent evidence in support of this is that reduced application of a convexity prior during perception of a hollow mask can lead to more veridical perception of such stimuli by schizophrenia patients. Furthermore, the extent of veridical perception by such patients was related to higher levels of hallucination and delusion, and to fewer days since last hospital discharge (Keane et al., in press). Moreover, this reduced sensitivity to the "hollow-mask illusion" has been shown, in dynamic causal modelling analyses of ERP and fMRI data, to be due to reduced top-down modulation of occipital lobe output in people with schizophrenia (Dima et al., 2009, 2010), as our theory predicts.

7. Difficulties for the hypotheses proposed and major aspects to be further developed

Hypotheses as general and abstract as ours cannot be confirmed or refuted by a single definitive experiment. Nevertheless, they can be strengthened or weakened by further evidence. For example, if further studies reveal many perceptual deficits in schizophrenia that are neither primary nor secondary consequences of impaired context-sensitive gain-control then our hypothesis concerning the functional impairments in schizophrenia would need to be amended. It will therefore be of great interest to see whether papers published as part of this *Frontiers* Research Topic reveal such deficits. If schizophrenia were shown to be due to impairments of mechanisms unrelated to context-sensitive gain-control then our hypothesis concerning the neuronal bases of schizophrenia could be rejected. Our hypotheses carry many implications concerning mechanisms that can be tested and developed by further work. Indeed, differences between our emphases now and those in Phillips and Silverstein (2003) show this clearly. Then we placed great emphasis on the role of NMDAR mediated neurotransmission as the mechanism for context-sensitive gain-control. Now we also place great emphasis on the role of PV interneurons because recent findings, such as those using optogenetic techniques, demonstrate that they are well-suited to that role (Atallah et al., 2012).

Most fundamentally, our hypotheses depend upon the distinction between context-sensitive gain-control and the driving signals that convey content. If that distinction were shown to be misleading or of no use then our perspective could be justifiably ignored. Though many arguments and findings have been offered in favour of such a distinction by ourselves and others, some researchers remain unconvinced, so we acknowledge that this fundamental distinction remains open to question.

Theories founded on the notion of optimal Bayesian inference have been challenged in various ways (e.g Jones and Love, 2011). For example, Bowers and Davis (2012) argue that such theories are difficult to test because post-hoc assumptions about priors or likelihoods can be used to explain almost anything. They also argue that human inference is often not optimal, and that the neurobiological evidence for such theories is weak. Clark (2013) notes that, being founded on the narrow goal of reducing prediction error, these Bayesian theories present a bleak desert-landscape

view of mental life. Though most commentators on his Behavioural and Brain Sciences target article support his enthusiasm for predictive processing, several do raise the above and other difficulties. Our perspective may help reduce some of these difficulties. First, one difficulty often raised concerns optimality, but we do not assume optimality. On the contrary, we argue that the conditions for optimality at the systems-level can be met only in simple cases (Phillips, 2012). Second, the neurobiological evidence for our hypotheses is strong and rapidly becoming stronger as it is supported by the optogenetic evidence that is now being used to explore the occurrence and mechanisms of contest-sensitive gain-control. Third, the theory of coherent infomax that underlies the hypotheses proposed in this paper avoids the desert-landscape criticism by emphasizing the objective of maximizing coherent inference rather than that of reducing prediction error (Kay and Phillips, 2010; Phillips, 2013). Finally, another difficulty facing any simple unifying theory is the need to explain the endless diversity of cognitive capabilities. Our perspective has to some extent met this need by showing that context-sensitive gain-control in visual size-perception varies greatly across people of different ages (Docherty et al. 2009), sex (Phillips et al. 2004), and culture (Docherty et al. 2008), but those studies are merely the first few steps into a largely unexplored territory.

Plenty of other difficulties and undeveloped possibilities remain. We cannot yet claim that all of the symptoms associated with schizophrenia are due to impairments of context-sensitive gain-control or their secondary consequences. Nor do we yet have adequate answers to questions concerning relations between schizophrenic impairments and the coordinate transformations that some see as a foremost function of gain-control. Is coordinate transformation impaired in schizophrenia or not? If not, why not? Is it because the form of gain-control involved in coordinate transformation is not context-sensitive in the way that the others are? Relations between classical neuromodulation and the more locally specific gain-control that we have emphasized also need to be further clarified. We expect them to be complex, and to operate in both directions. There is also much that needs to be clarified concerning the full range of schizophrenia-related deficits in visual perception. For example, it is well-established that these include changes in visual masking (Green et al., 2011). Such deficits may be related to the reduced temporal precision shown by Hancock et al. (2008) and to the impairments of PV inhibitory interneurons emphasize above, but we have not yet examined that possibility adequately.

Overall, our view of the difficulties and immaturities faced by our perspective is that they offer far more opportunity for healthy growth than they do for fatal decline. It will be of great interest to see whether developments over the coming years justify that optimism.

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Conflicts of interest

The authors declare no potential conflicts of interest.

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