symptoms of schizophrenia. We have just argued that the multiplicative interaction between driving and contextual connections is important to avoid hallucinations, since hallucinations may occur if feedback *drives* neurons in early sensory areas that are not activated by bottom-up. This multiplicativity may be lost in schizophrenia; recent imaging work demonstrates that the primary auditory cortex is activated by auditory hallucinations in schizophrenic patients (Dierks et al. 1999). This implies that feedback in schizophrenia is *too strong*, because it can create activity patterns in sensory areas that are not supported by the sensory organ itself – and contradicts Phillips & Silverstein's (P&S's) hypothesis that the main deficit in schizophrenia is a weakness of contextual modulation.

We conclude that a general weakness of contextual effects cannot be the only deficit in schizophrenia. Mechanisms other than contextual modulation must be disturbed in the communication between neurons in the same and different brain areas. Unfortunately, we still know too little about these interactions, even in normal subjects. Some hold, for example, that they are carried by synchronous neuronal rhythms (Phillips & Singer 1997a; Singer & Gray 1995), whereas others argue that they are rather associated with the modulation of firing rates (Desimone & Duncan 1995; Lamme & Roelfsema 2000), although these possibilities are not mutually exclusive. The target article is an important contribution because it pinpoints our lack of knowledge about how neurons in different cortical areas exchange information. Moreover, it provides an inspiration to study disturbances in the neuronal interactions to gain insight in the pathophysiology of schizophrenia.

No blind schizophrenics: Are NMDA-receptor dynamics involved?

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Abstract: Numerous searches have failed to identify a single co-occurrence of total blindness and schizophrenia. Evidence that blindness causes loss of certain NMDA-receptor functions is balanced by reports of compensatory gains. Connections between visual and anterior cingulate NMDA-receptor systems may help to explain how blindness could protect against schizophrenia.

Phillips & Silverstein (P&S) have pieced together a plausible and detailed connection between NMDA-receptors and schizophrenia. Our commentary is intended to illustrate the idea that receptor hypofunction is a dynamic process that in certain cases may lead to compensatory and protective neural circuitry. We first consider implications of research on early sensory deprivation, and then provide substantiation for our claim (Sanders et al. 2002) that blind people do not become schizophrenic.

Variation in sensory experience has important effects on cerebral architecture and connectivity (overview in Geary & Huffman 2002). Some of this impact applies directly to blindness and NMDA-receptor structure and function. For example, when marmosets undergo monocular eyelid suture, their ocular dominance columns exhibit suppressed NMDA-receptor NR1 subunit immunoreactivity (Fonta et al. 2000). This suggestion of impaired receptor integrity is consistent with reductions in NMDA-evoked, but not baseline, calcium uptake in the striate cortex of dark-reared kittens (Feldman et al. 1990). Dark-rearing also increases sensitivity of rats' visual cortex NMDA-receptors to certain chemical antagonists (Fathollahi & Salami 2001), which may be a reflection of receptor loss or abnormality.

The impact of visual deprivation on NMDA-receptors probably extends beyond the occipital cortex. Given the substantial role of the anterior cingulate cortex (ACC) in cognitive coordination and in schizophrenia (Sanders et al. 2002), it is noteworthy that ACC and primary visual cortex have strong physical (Vogt & Miller 1983) and functional (Nishijo et al. 1997) connectivity mediated by glutamate transmission and NMDA-receptors (Sah & Nicoll 1991). As a result, hypofunction in visual cortex may lead to diminished input for and altered structure or function of NMDA-receptors in the ACC. Consistent with this possibility, the ACC participates in the generation of visual images (Deiber et al. 1995), and the visual images of blind people suffer from deficiencies in dynamic grouping and context sensitivity (DeBeni & Cornoldi 1988), which the target article attributes to reduced ion flow in NMDA-receptors.

Despite indications of widespread NMDA abnormality in blind people, there is no evidence that they develop the severe cognitive coordination problems characteristic of some types of schizophrenia. On the contrary, blind people seem to be completely protected. Five independent searches, varying considerably in scope, methods, and population, failed to identify even one well-defined co-occurrence of total blindness and schizophrenia (Abely & Carton 1967; Chevigny & Braverman 1950; Feierman 1982; Horrobin 1979; Riscalla 1980). We dedicated portions of 2000 and 2001 to e-mail and postal mail surveys of relevant professionals; e-mail and telephone discussions with officials of health, mental health, blindness, and schizophrenia organizations and research institutes; and extensive keyword probes of Medline, PsychINFO, and ScienceDirect databases. Some ambiguity was introduced by very low return rates for our surveys, but the consistent result of all these inquiries was that no instance of totally blind/schizophrenic co-occurrence was found.

How could blindness protect against schizophrenia? Our hypothesis (Sanders et al. 2002) centers on the idea that certain compensations in the ACC for loss of visual input may provide "immunity." Blindness leads to neural reorganization and restructuring (Hamilton & Pascual-Leone 1998; Liotti et al. 1998). Psychologically, these cortical changes allow the blind to achieve normal cognitive development (Warren 1994) despite formidable challenges (e.g., Sandler & Hobson 2001). One example of the compensatory reactions to blindness is the development of above-average verbal memory (Decker & Koole 1992).

We believe that some of these blindness-induced neural and psychological compensations involve the dynamics of NMDA-receptor function. Evidence of deprivation-induced receptor hypofunction is balanced by a report of upregulation of NMDA-receptor 1A subunits in optic and intermediate gray layers of superior colliculus resulting from peripheral blindness (Vizuete et al. 2001). This upregulation led to an increase in corticocollicular synapses as a compensation for the loss of retinocollicular interaction. In the same vein, dark-rearing forestalls the normal upregulation of NMDA-receptor 2A subunits in striate cortex (Quinlan et al. 1999). This interference with normal receptor elaboration has the paradoxical, or compensatory, effect of enhancing NMDA-receptor activity, ultimately prolonging the critical period for plasticity and modulation in the visual cortex (Fox et al. 1999). Such trade-offs between loss and gain in visual system NMDA-receptors of blind people may help explain the mature viability and reorganization of a sensory region deprived of its primary afferents (Breitenseher et al. 1998).

As was the case for losses discussed above, there is reason to believe that blindness-induced NMDA-receptor gains in primary visual system are matched in other regions, particularly the ACC. A pertinent example is the report of a larger mismatch negativity (MMN) evoked-potential response to deviant auditory stimuli in blind than in sighted humans (Kujala et al. 1995). This demonstration of enhanced context sensitivity in the blind stands in stark contrast to the diminished MMN (mismatch negativity) observed in schizophrenics, and also in control samples administered the NMDA-receptor antagonist ketamine (Umbricht et al. 2000).

Strong involvement of ketamine in ACC function is firmly established, and the ACC is a relatively late (top down?) generator of MMN (Waberski et al. 2001). It is reasonable to speculate that the dynamics of blindness-induced NMDA-receptor hypofunction in visual cortex extends to NMDA-receptor gains in the ACC, which in turn increase some types of context sensitivity, perhaps ultimately resulting in protection against schizophrenia.

In the light of these results, the answer to point 11 in P&S's concluding section – "Is the molecular and regional diversity of NMDA receptor channels . . . crucial?" (target article, sect. 8) – is likely to be "Yes!" (see de Belleroche et al. 1998 for direct evidence). The impression of dynamic, heterogeneous, and compensatory processes produced by research on visual deprivation is enhanced when deafness is added to the picture. Loss of auditory input produces a pattern of loss and gain in NMDA-receptor function in some ways similar to and in other ways different from the effects of dark-rearing or blindness (e.g., Nakagawa et al. 2000; Oleskevich & Walmsley 2002). Most unlike the effects of blindness, deafness does not serve to prevent schizophrenia (e.g., Schonauer et al. 1999).

Many of the issues raised by P&S may be better understood following certain comparisons among blind, deaf, schizophrenic, and control samples. For example, how might blind people respond to ketamine antagonism of their ACC NMDA-receptors? It would be especially interesting to extend to blind and deaf samples the work on cortical rhythms reviewed in section 5 of the target article. Patterns of beta and gamma frequencies, and their modulation by ketamine, may reveal differences in local and top-down cognitive coordination in blind versus deaf people, thus helping explain the dramatic difference in their susceptibility to schizophrenia.

Phenomenology, context, and self-experience in schizophrenia

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Abstract: Impairments in cognitive coordination in schizophrenia are supported by phenomenological data that suggest deficits in the processing of visual context. Although the target article is sympathetic to such a phenomenological perspective, we argue that the relevance of phenomenological data for a wider understanding of consciousness in schizophrenia is not sufficiently addressed by the authors.

Phillips & Silverstein (P&S) propose an innovative model of the characteristic cognitive disorganization of schizophrenia, based on neurobiological, pharmacological, and cognitive data. The authors also refer to the classic psychiatric writings of Matussek (1952/1987) and Conrad (1958), who adopt a Gestaltist perspective and describe subjective experience in schizophrenia in detail. Although we applaud the mention of such Gestaltist work with its emphasis on phenomenological data, we believe that the theory of P&S neglects important aspects of consciousness in schizophrenia that are central to the understanding of the condition.

In Anglophone psychiatry, *phenomenology* generally refers to the study of observable signs and symptoms. In philosophy and phenomenological psychiatry, however, *phenomenology* refers to the systematic study of conscious experience from a first-person perspective and is tied to certain philosophical positions regarding mind and its relationship to the world. We believe that inclusion of a phenomenological perspective (in the second sense) is essential to gain insights into the cognitive abnormalities and their wider relevance for understanding the schizophrenic condition (Sass & Parnas, in press a).

Gurwitsch (1964) offers a phenomenological analysis that may help to clarify the subjective dimension of these disorders and the role of context in consciousness. In Gurwitsch's view, the field of consciousness always involves a "theme," "thematic field," and "margin" of awareness. Gurwitsch's first domain, the "theme," is that which engrosses the subject, stands in the focus of his attention, and "upon which his mental activity concentrates" (p. 4). The theme is characterized by the kinds of relationships classically described by Gestalt psychology: Here, each constituent "exists in the very qualifications by which it is defined and made to be that which it is in a given case, only in conjunction with, and determined by, co-constituents" (p. 139). The second domain, the "margin," is the realm of objects of awareness that are simultaneously present to consciousness but not experienced as relevant to the focal theme; it includes elements of ongoing bodily existence, the perceptual surround, and the stream of consciousness (p. 11). The third domain – a kind of middle realm – is that of the "thematic field," defined as "the totality of facts, co-present with the theme, which are experienced as having material relevancy or pertinence to the theme" (p. 55).

Constituents of the thematic field are not merely copresent; they hang together in a mutually implicative way, and have relevance for the focal theme. Thus, the *way* in which each of these constituents is experienced is a function of some larger unifying significance that also determines the *aspect* of the theme that will emerge as significant. Gurwitsch (1964) speaks here of "unity by relevancy," which is bound up (as both source and product) with the unity of *context* (p. 341); it can be distinguished from the even tighter form of unity inherent in "Gestalt-coherence."

The main disturbance in schizophrenia, according to P&S, concerns the capacity for "context-processing." From a phenomenological and experimental perspective, a disturbance in context-processing is most obvious at the level of context that Gurwitsch calls the "the thematic field," because schizophrenia patients are not deficient in the ability to perceive basic Gestalts (Knight et al. 2000; Sass, in press). The work of Matussek (1952/1987) and Conrad (1958) supports this view. Examination of Matussek's clinical illustrations shows that there is seldom, if ever, a breakdown of the basic spatial form; indeed, the integrity of the visual object may even be heightened as it stands out with special clarity while the background recedes in dullness and indifference (Matussek 1952/1987, p. 92). The main perceptual alteration Matussek emphasizes is a "loosening of the natural perceptual context" or of the "coherence of perception."

Impairment in context-processing at the level of the thematic field has wide implication for the understanding of consciousness in schizophrenia. According to Gurwitsch (1964), the "thematic field" determines the "*perspective* under which, the *light and orientation* in which, the *point of view* from which" the theme appears to consciousness (p. 359). Accordingly, weakening of the "thematic field" is associated with a loosening of perceptual context that may alter the organization or salience of the theme. The phenomenological evidence suggests that this is so. Matussek, for example, describes everyday objects that are framed in isolation, and thus come to seem strange or to acquire exaggerated and often enigmatic symbolic "weighting" as a result of the "loosening of the natural perceptual context" (Matussek 1952/1987).

Relevancy relationships (characteristic of the thematic field) are the kind that are most directly related to the ongoing *projects* or *concerns* of the subject; for this reason they may be especially closely linked to fundamental aspects of *self*-experience, that is, to the underlying sense of existing as a vital and unified *subject* of awareness or first-person perspective, which has been referred to as "ipseity" (from the Latin *ipse*, which means *self* or *itself;* Sass 2000; Sass & Parnas, in press b). The typically schizophrenic alterations of the cognitive/perceptual field are, in fact, usually accompanied by disruptions in this most basic sense of selfhood (Klosterkoetter et al. 1997; Møller & Husby 2000; Parnas et al. 1998). Such a patient may complain of an "inner void," of "painful distance to self," of being "occupied by, and scrutinizing, my own