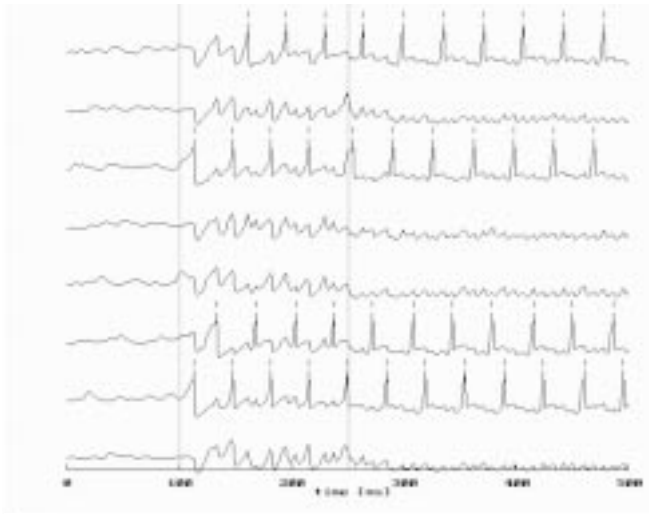
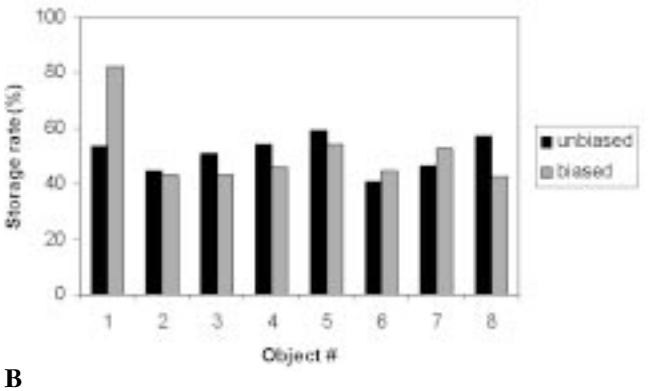
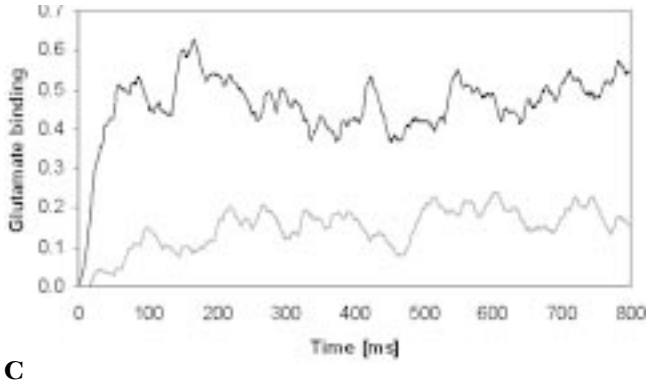


A



B



C

Figure 1 (Raffone et al.). NMDA-dependent biased competition effects in visual working memory storage. (A) Typical evolution of membrane potentials of eight model neurons from eight parietal assemblies coding for eight different objects (stimulus onset is at 100 msec, and offset at 250 msec; only four objects are maintained after stimulus offset). (B) Percent storage rate of eight objects with (grey bars) and without (black bars) bias toward Object 1, over 200 trials with a storage capacity of about four objects. (C) Glutamate binding at NMDA synapses for attended (black curve) and unattended (grey curve) objects. See text for further explanations.

pending on their top-down saliency. They can, therefore, implement a multiplicative computational scheme in attentional processing, as in Bundesen's (1990) TVA.

We have simulated this NMDA-dependent gain effect in visual working memory storage (Raffone et al., in preparation). In the model, separate objects are encoded by disjoint sets of recurrently-coupled neural assemblies located in the inferotemporal cortex, parietal cortex, and prefrontal cortex. Neural assemblies in parietal cortex receive top-down NMDA signals from *control assemblies* with a differential firing rate located in a prefrontal area.

In the simulation series shown in Figure 1, the cortical network model was presented with displays of eight objects. Given that on average only four objects are stored in terms of reverberations in the absence of any attentional bias (Raffone & Wolters 2001), the storage rate for each object is about 50%. Figure 1A shows the typical evolution of membrane potentials (firing patterns) of eight parietal neurons coding for different objects, with interneuron time-lags reflecting between-pattern segregation. In Figure 1B, the storage rate of eight objects over 200 trials is shown with and without attentional bias toward Object 1. Note the higher storage rate of Object 1 with the amplifying effect of NMDA function (in terms of latent glutamate binding, see Fig. 3 in the target article) added to the parietal assembly coding for it, as compared with the unbiased condition. All the other structural and dynamic parameters are kept constant across the two conditions. Figure 1C shows the evolution of latent NMDA synaptic signals (amount of bound glutamate modeled in terms of a dual exponential with rise time of 5 msec and decay time of 50 msec) to target and distractor assemblies in the biased attentional weight condition.

As shown by our simulations, an important property of NMDA signals is that they are voltage-dependent, and therefore are enabled only in the presence of bottom-up input (sensory evidence). In our model, this dynamic property is also crucial to prevent spurious activation spreading to irrelevant neurons by feedback connections from prefrontal cortex during maintenance. In this case, NMDA signals are generated at the level of recurrent connectivity intrinsic to neural assemblies in posterior areas, and top-down signals from prefrontal cortex selectively act on non-NMDA input-activated assemblies with a sufficient amount of intrinsic glutamate binding. Therefore, reverberations for maintenance only capture input-activated neurons in feature and location dimensions. The absence of NMDA from this circuitry would imply either reduced maintenance capacity or the emergence of hallucinatory neural representations.

If NMDA synaptic systems are impaired in schizophrenia, as suggested by P&S in the target article, and if NMDA synapses play a crucial role in attentional selection and control of storage and maintenance in visual working memory, as suggested by our model, then differences between groups of schizophrenic patients and control groups are predicted in cognitive tasks with interactions between visual working memory and selective attention. Similar functional and pathological principles may be involved in auditory (verbal) working memory and selective attention. Our model also predicts hallucinations as a result of spurious activation spreading from prefrontal cortex to posterior cortical areas under the effect of NMDA-antagonists, and, following P&S, in schizophrenia.

Why do schizophrenic patients hallucinate?

Pieter R. Roelfsema[a] and Hans Supèr[a, b]

[a]*The Netherlands Ophthalmic Research Institute, 1105 BA Amsterdam, The Netherlands;* [b]*Graduate School of Neurosciences Amsterdam, Department of Visual System Analysis, Academic Medical Center (UvA), 1100 AA Amsterdam, The Netherlands.* **{p.roelfsema;h.super}@ioi.knaw.nl**

Abstract: Phillips & Silverstein argue that schizophrenia is a result of a deficit of the contextual coordination of neuronal responses. The authors propose that NMDA-receptors control these modulatory effects. However, hallucinations, which are among the principle symptoms of schizophrenia, imply a flaw in the interactions between neurons that is more fundamental than just a general weakness of contextual modulation.

The target article distinguishes between "primary input" and "contextual input" onto a neuron. Primary input drives the cell and

https://doi.org/10.1017/S0140525X03410029 Published online by Cambridge University Press

is generally attributed to feedforward connections that propagate activity from lower to higher areas (Felleman & Van Essen 1991). Contextual input, on the other hand, does not activate a neuron, but rather modulates its response. One source of contextual effects in vision is the stimulus context, because properties of the stimulus outside the receptive field can modify neuronal responses. These contextual effects are usually attributed to preattentive vision (Lamme & Roelfsema 2000). Task requirements are another source of contextual effects that depend on shifts of visual attention (Roelfsema et al. 2000).

Both types of contextual influences are particularly strong for neurons that are well driven by the visual stimulus, and much weaker for cells that receive little bottom up activation (Kapadia et al. 1995; Knierim & Van Essen 1992; McAdams & Maunsell 1999; Zipser et al. 1996). We agree with the target article that contextual effects appear to multiply the effect of driving connections, by some factor. Here we focus on the multiplicativity of this interaction, and argue that it is important for the specificity of both preattentive and attentive response modulation.

Visual search is an example of an attention-demanding task that depends on interactions between cortical areas, and that is impaired in schizophrenia (Lubow et al. 2000). In visual search, the identity of an item is given and its location has to be determined. This implies an interaction between ventral stream areas encoding the identity of the target item, and areas in the dorsal stream, as well as early visual areas that encode locations. A scheme that incorporates the essential ingredients of contemporary models of search is indicated in Figure 1. Three areas have been indicated, at different levels of the visual cortical hierarchy. In this simplified scheme, two features (a and b) are represented in each of the areas. Feedback connections interconnect neurons with a similar feature preference. Neurons that are driven by feedforward connections are indicated as black circles. Search for a particular target feature (e.g., feature a) can be implemented by feedback from higher areas to enhance the activity neurons in lower areas that have the target feature in their receptive field (Roelfsema et al. 2000; van der Velde & de Kamps 2001).

Figures 1B and 1C compare the effects of multiplicative (modulatory) and additive (driving) feedback. If feedback is multiplicative, as in Figure 1B, only neurons that receive bottom-up support from feedforward connections are influenced by it, and feedback does not spill over to neurons without a matching feature in their receptive field (stippled connections in Fig. 1B are disabled since there is no bottom-up input to these cells). When the search has been completed, the location of the target item is encoded by a response enhancement in early visual areas, which can be read out by areas of the dorsal stream (van der Velde & de Kamps 2001). Figure 1C shows that this focusing of activity at the location of the target item cannot be achieved by additive feedback (driving connections), because it would also activate neurons at locations of distractors (e.g., connection 1 in Fig. 1C). Moreover, additive feedback can even activate neurons at locations where there are no objects at all (connection 2). Grossberg argued that feedback therefore has to be multiplicative, to prevent hallucinations (Grossberg 1999). Models of "preattentive" texture segregation have also exploited the virtues of multiplicative feedback, to enhance activity in early visual areas evoked by a figure over activity evoked by the background (Roelfsema et al. 2002).

The proposal of the target article that contextual effects are mediated by NMDA-receptors would account for the multiplicative interaction between contextual and driving connections (Fox et al. 1990). Current can flow only through NMDA-channels of neurons that are sufficiently depolarized by driving connections to remove the Mg-block. We note, however, that certain anesthetic agents not acting on NMDA-receptors but operating through different routes, also interfere with contextual modulation without an effect on driving connections (Lamme et al. 1998; Pack et al. 2001). Nevertheless, we agree that the possibility that NMDA-receptors are important for contextual modulation is exciting and worth testing.

But what about hallucinations? They are among the defining

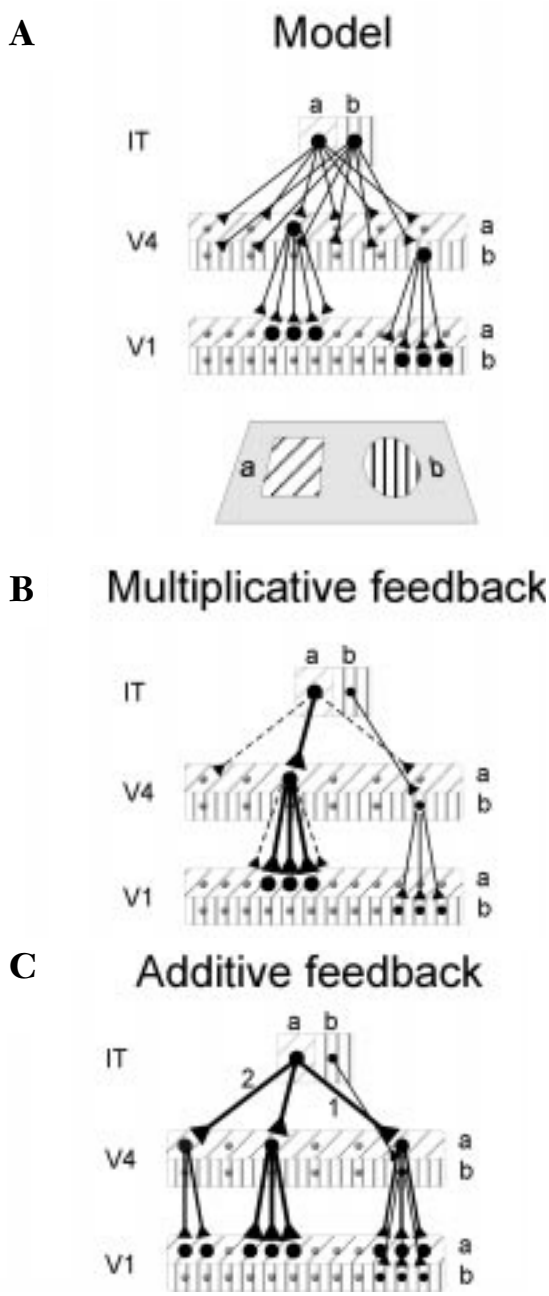


Figure 1 (Roelfsema & Supèr). Involvement of feedback connections in visual search. (A) In models of visual search, feedback connections are assumed to interconnect neurons with a similar feature preference. Two features (*a* and *b*) are represented in three areas of the temporal stream of the visual cortex. In reality, more stages are interposed between the primary visual cortex (area V1) and the inferotemporal cortex (area IT). Neurons that are activated by the stimulus below (by feedforward, driving connections, not shown) have been indicated as black circles. Neurons not activated by the visual stimulus are indicated as small gray circles. (B) Multiplicative feedback. Connections to neurons not activated by the input have no effect (stippled connections). Visual search for feature *a* can be implemented by feedback from area IT, enhancing neuronal responses to the target feature "*a*" (thick connections) in lower visual areas. In retinotopic areas, the response enhancement occurs at the target object's location, and this solves the search task. (C) Additive feedback *activates* neurons at lower hierarchical levels that are not activated by bottom up. It activates neurons at the location of the distractor object (connection 1), and even at locations without an object (connection 2), causing hallucinations.

https://doi.org/10.1017/S0140525X03410029 Published online by Cambridge University Press

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?

Glenn S. Sanders[a], Steven M. Platek[b], and Gordon G. Gallup, Jr.[a]

[a]*Department of Psychology, State University of New York at Albany, Albany, NY 12222;* [b]*Department of Psychology, Drexel University, Philadelphia, PA 19102.* **steven.m.platek@drexel.edu**
http://www.pages.drexel.edu/~smp43 **gallup@csc.albany.edu**
http://www.albany.edu/~gallup **http://www.evolutionarypsych.com**

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).

https://doi.org/10.1017/S0140525X03410029 Published online by Cambridge University Press