

## PERCEPTUAL ORGANIZATION IN SCHIZOPHRENIA: PLASTICITY AND STATE-RELATED CHANGE

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Perceptual organization (PO) impairments have been repeatedly demonstrated in schizophrenia. The extent to which these impairments can be reduced or eliminated, however, has received less attention, and evidence on this issue has not been previously reviewed. The literature suggests that whether normal experience-dependent change in perceptual organization occurs in schizophrenia depends on factors such as: stimulus grouping strength, extent of practice, type of cues upon which top-down feedback can be generated, and patient characteristics (trait and state). Therefore, the purpose of this paper is to review and synthesize the available evidence on plasticity and other forms of change in PO in schizophrenia, and to relate it to current data and theories on plasticity, including perceptual learning (PL) in healthy people. This can clarify the computational and neural mechanisms involved in experience-dependent and state-related aspects of PO in schizophrenia, and also contribute to a greater understanding of the mechanisms involved in normal PL. A major finding that emerges from a review of the data is that the conditions under which PL of PO does *not* occur in schizophrenia closely parallel the conditions under which PO is reduced in a single test administration. That is, when stimulus-driven cues to grouping are strong, PL of PO occurs in patients; in contrast, when top-down feedback is required to organize novel or weakly grouped stimuli, PL of PO tends *not* to occur in patients. Moreover, even with strongly grouping stimuli, change tends to occur only via repetition; when processing of more abstract cues is required to generate top-down feedback, change tends not to occur. In addition, within-session PL in people with schizophrenia appears to be more impaired than learning over multiple days, supporting the

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separability of fast and slow plasticity mechanisms; however, more research with a larger class of stimuli is needed on this issue.

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## 1. INTRODUCTION: PERCEPTUAL ORGANIZATION AND SCHIZOPHRENIA

Perceptual organization (PO) “is the process by which particular relationships among potentially separate elements (including parts, features and dimensions) are perceived (selected from alternative relationships) and guide the interpretation of those elements... in sum, how we process sensory information in context” (Pomerantz and Kubovy, 1986, p. 36). Originally the focus of the Gestalt psychologists – such as Wertheimer, Kofka and Köhler – PO has been studied extensively since the cognitive revolution in the 1960s. Work done during this second wave of interest has produced an enormous number of insights: that PO can arise from both bottom-up and top-down effects (Quinn and Bhatt, 2009); that it operates from early to later phases of perception on multiple forms of representations (Palmer, Brooks and Nelson, 2003); that learning and memory play a role (Fine and Jacobs, 2000; Kimchi and Hadad, 2002); that there are grouping principles other than those identified by the Gestalt psychologists (Palmer, 1999, pp. 259–261); that it develops over time until early adulthood (Kovács, 2000; Kovács et al., 1999); that there are neural “signatures” such as synchrony within the beta and gamma bands (Uhlhaas et al., 2009) or “negativity closure” (as revealed by electrophysiological recordings) (Sehatpour et al., 2006); and that, as revealed by functional magnetic resonance imaging (fMRI), grouping processes involve activity in specific brain regions and networks (e.g., V1–V4, frontal and parietal attention-control regions and their interaction with visual areas) (Altmann, Bühlhoff and Kourtzi, 2003; Bouvier and Treisman, 2010; Ciaramelli et al., 2007; Kourtzi et al., 2003; McMains and Kastner, 2010; Silverstein et al., 2009). Research also indicates that PO is impaired in certain psychiatric and ophthalmologic conditions such as schizophrenia and amblyopia (Silverstein, 2010).

One disorder in which PO impairments have been consistently demonstrated is schizophrenia. Schizophrenia is a severe psychiatric disorder that occurs in 1% of the population worldwide and is typically diagnosed in late adolescence or early adulthood. It often leads to lifelong disability in social and vocational functioning, and is characterized by a mixture of positive, negative and disorganized symptoms (American Psychiatric Association, 1994; Silverstein, Spaulding and Menditto, 2006). Positive symptoms are those that are *added* on to normal functioning and include auditory hallucinations and paranoid beliefs. Negative symptoms reflect a *reduction* in normal functioning, and include a reduction in anticipatory pleasure, amount of speech, amount of social interaction, and facial expression of emotion. Disorganized symptoms reflect a *fragmentation* in functioning; these include incoherent speech and thought, out-of-context gestures and movements, and facial expressions inappropriate to what is being thought or felt. While schizophrenia is diagnosed on the basis of these symptoms and a decline in functioning, perceptual deficits are core features of the illness, especially those having to do with the organization of the proximal array (Chapman, 1966; Butler,

Silverstein and Dakin, 2008). Studies of PO in schizophrenia – which go back to the 1960s (Snyder, 1961; Snyder, Rosenthal and Taylor, 1961) with a rapid increase since the 1980s – have been reviewed elsewhere (e.g., Uhlhaas and Silverstein, 2005), but some of these findings are worth recapitulating as they are particularly robust and will aid the evaluation of other data discussed below. The key findings can be summarized as follows.

1. PO impairment is most pronounced when the stimuli are novel, fragmented, and/or noisy, when top-down input is required, and when strong stimulus-driven cues are lacking;
2. PO impairment is found mainly among patients who have a long history of poor premorbid (pre-illness) social functioning (e.g., few friends or intimate relationships in childhood and adolescence);
3. The presence of PO impairment predicts poor prognosis;
4. PO begins as normal in people at high-risk for the disorder and even among patients at their first psychotic episode, but deteriorates thereafter;
5. It is significantly correlated with reduced organization in other domains such as thought and language (e.g., disorganized and incoherent speech);
6. It is most pronounced when patients have moderate-high levels of disorganized symptoms, and approach normal levels as these symptoms resolve during treatment;
7. It is unrelated to medication dose and has been found in medicated and unmedicated patients;
8. It is not due to the general performance deficiencies and poor motivation found in many patients, since patients performed *better* than control subjects on certain tasks where PO could impair task performance;
9. In EEG studies, the behavioral impairment is associated with reduced amplitude of a waveform that has been termed “negativity closure” (NCI) (Sehatpour et al. 2006), as well as a reduction in synchronized oscillations within the beta and gamma bands (Spencer et al., 2003, 2004; Uhlhaas et al., 2006a); and
10. In fMRI studies, patients demonstrated reduced activity in visual cortex regions relevant to PO (e.g., V2–V4) and object-based attention (e.g., frontal and parietal regions) (Silverstein et al., 2009).

Despite extensive documentation of PO impairment in schizophrenia, far less is known about the extent to which it can be improved in the short- or long-term. The purpose of this paper is to review literature on this issue. Understanding the capacity for change in PO in schizophrenia will elucidate the extent to which basic perceptual processes can be ameliorated in this disorder, and also contribute to a greater understanding of how PO and perceptual learning (PL) occur in healthy individuals. The latter is important because, despite an emerging understanding of PL, many questions about its mechanisms remain (Yotsumoto, Watanabe and Sasaki, 2008).

The discussion below is divided into two parts. In the first part, *non-clinical* literature on PL and PO is reviewed with a special focus on those findings relevant to interpreting findings on change in PO in schizophrenia. In the second part, research on improvement in PO in schizophrenia is reviewed, with links being made to what these data may mean in light of what is known about plasticity, PL, and state-related change from the non-clinical literature.

## 2. PERCEPTION AND LEARNING

There is an increasing appreciation that perception is an experience-dependent process (Sagi, Kovács and Racsmány, 2009). Indeed, some have drawn the profound conclusion that perception cannot even be separated from learning; that the two are intimately linked. For example, Laurent (2010) noted that: a) perceptual recognition would not exist without the influence of stored templates and representations to guide classification, comparison and interpretation; b) a function of learning is to increase the efficiency of perceptual processing; and c) the mechanisms underlying perception should express the requirements imposed by learning, storage and recall and vice versa. As evidence, the mechanisms underlying both PO and PL (and perhaps other forms of learning as well) plausibly involve adaptive changes in connection with strengths between neurons exhibiting correlated firing activity (Fuster, 2005; Phillips and Singer, 1997; Kay and Phillips, 2010). These changes may underlie the representation of spatiotemporal regularities in the distal environment (Löwel and Singer, 2002) – a form of representation for which there is evidence of impairment in schizophrenia (Hemsley, 1994).

There is now a large body of experimental data demonstrating PL in healthy people. To date, learning effects have been demonstrated for vernier discrimination (Poggio, Fahle and Edelman, 1992), common object recognition (Furmanski and Engel, 2000), complex pattern discrimination (e.g., Fine and Jacobs, 2000; Sowden, Davies and Roling, 2000), visual search (Ahissar and Hochstein, 1996), and texture discrimination (Karni and Sagi, 1991), among others. Training improvements have been shown to last hours and even years later (Karni and Sagi, 1993). Until recently, however, there has been relatively little research focused on experience-dependent improvement in PO (though see below). For example, a search on [www.pubmed.gov](http://www.pubmed.gov) (as of 27 October, 2010) revealed that the intersection of “perceptual learning” and “perceptual organization” yielded only 2 items even though each term by itself generated over 500 entries! Despite this, we show that there actually is a reasonable amount of data on the topic. Before diving into the relevant literature, we first discuss the proposed mechanisms of PL.

### *2.1. Mechanisms of perceptual learning*

Although we are not yet at a point where a single, comprehensive model of PL can be fully specified (Herzog and Fahle, 2002), recent work has begun to identify biologically plausible mechanisms for learning. We do not attempt to summarize the entire large and growing literature on this issue here, but rather, discuss only those views that we believe are of relevance to understanding PL of PO in schizophrenia. One model that is particularly relevant is that of Lu and Doshier (2009). These authors suggested that PL involves two mechanisms: external noise exclusion and stimulus enhancement. Both are relevant to learning PO, especially in contour integration tasks and others where background distractors are present. Both mechanisms are seen as reflecting re-weighting of stable early sensory representations for later processing and augmented Hebbian learning. This is similar to earlier views that PL involves the enhancement of the integration of relevant object features and their segmentation from background noise (e.g., Brady and Kersten, 2003; Gilbert, Sigman and Crist, 2001; reviewed in Kourtzi,

2009). Lu and Doshier's (2009) view is also supported by recent fMRI data indicating that grouping mechanisms that enhance phenomenological salience, and competitive interactions that inhibit phenomenological salience of stimuli outside the attended group, occur simultaneously in early visual cortex and V4 (McMains and Kastner, 2010). Moreover, electrophysiological studies indicate that PL is related to increases in: the synchronization of oscillatory activity of neurons responding to the features of the target object; and de-synchronization of neural responses coding distractor elements (Erickson, Jagadeesh and Desimone, 2000; Jagadeesh et al., 2001; Phillips and Singer, 1997, Teich and Qian, 2010). Finally, this theory is consistent with evidence that long-range, excitatory, spatial interactions between neurons are experience-dependent and that both excitatory and inhibitory effects are involved in PL and can be changed with practice (Zenger and Sagi, 2002).

Functional MRI (fMRI) studies have generated other important information on the neural mechanisms underlying PL. For example, fMRI studies suggest that tuning of activity in visual areas can occur based on top-down feedback from parietal and frontal areas (Roelfsema, 2006; Büchel, Coull and Friston, 1999). It has also been shown that – with increased object familiarity – fewer neurons respond (as observed via fMRI BOLD signal decreases) (Yotsumoto, Watanabe and Sasaki, 2008) and neurons become more narrowly tuned (Rainer and Miller, 2000). Learning to better utilize basic feature information (e.g., vernier acuity and texture segregation) may involve changes primarily in V1 or even earlier, whereas learning for more complex tasks like visual search – which generalizes over tasks, locations, size, and eyes (Sireteanu and Rettenbach, 2000) – typically involves changes in higher areas such as IT (although changes have been observed in early visual areas as well in more complex PL tasks, cf., Ahissar and Hochstein, 1996; Furmanski and Engel, 2000; Sheinberg and Logothetis, 2002).

In addition to these perceptual mechanisms, Doshier and Lu (1999, 2009) hypothesized the importance of a decision or response unit in which the reweighting of specific representations during decision processes is a determinant of observed PL. This view is supported by evidence that attention-gated, top-down mechanisms modulate responses in V1 by retuning read out signals, rather than by changing the encoding of the stimuli (Kourtzi, 2009; see also Ahissar et al., 1998). Doshier and Lu's hypothesis fits well with that of Sinha and Poggio (2002), who posit a mechanism operative in PL wherein the visual system “learns” an algorithm specific to a class of objects by associating an ideal output to the input. Indeed, it has been proposed that modifications at the output level account better for PL data than modifications of sensory representations (Ahissar et al., 1998). It seems that the most likely scenario is that both lower and higher cortical areas are involved in learning, with a critical determining factor being task difficulty. According to reverse hierarchy theory, easy learning begins in higher-level areas whereas learning more difficult perceptual discriminations can result in access to, and changes in, activity in lower areas (and also in lack of transfer to novel stimuli) (Ahissar, 1999; Schiltz et al., 1998). An implication of these data is that PL does not involve *only* changes in activity (e.g., firing rates) in sensory cortex, but can also make use of fine-tuning of decision and response processes. This is relevant to schizophrenia since reduced activity in brain regions subserving decision and response processes has already been demonstrated during performance of a PO task (Silverstein et al., 2010b), thereby further suggesting

the possibility that patients' impairments in PL of PO could involve perceptual *or* post-perceptual processes, or both.

An important process relevant to PL is sleep. Karni et al. (1994), and Mednick et al. (2002) demonstrated that REM and slow-wave sleep between training sessions are important for consolidation to occur. However, within-session practice effects have also been observed and so not all learning requires sleep. Stickgold, James and Hobson (2000) proposed three stages in PL of a visual discrimination task: 1) within-session practice effects; 2) improvement due to early night slow wave sleep (SWS); and 3) improvement due to late night rapid eye movement (REM) sleep. Below, we will argue that – although sleep is relevant to understanding learning – it likely *cannot* explain differences in PL of PO between people with schizophrenia and other people.

## 2.2. Learning of perceptual organization

A number of studies suggest that PO can be improved with training. For example, Li and Gilbert (2002) demonstrated that when a naïve participant was trained to detect a collinear path composed of spatially segregated edge segments, the individual could tolerate a much larger inter-element spacing over the course of 12 daily training sessions. Although change occurred after day 1, the majority of the change above baseline occurred between days 6–12. Also, of note was that this improvement occurred primarily when the contour element spacing was of intermediate magnitude. When the elements were further apart ( $>6$  deg), no amount of training could lift performance from chance; when the spacing was small ( $\sim 0.8$  deg), the contour was already close to popping out so that performance was near ceiling at the task outset. This is important: it suggests that any impairments in learning PO should be most apparent when the elements group together, but only weakly. In a later contour integration study, Li, Piëch and Gilbert (2008) showed that both behavioral performance and V1 activity in monkey increased with training. These training effects were abolished when potential top-down influences were eliminated with anaesthesia, underscoring the high value of top-down influence. Also, Pennefather et al. (1999) reported small improvements in contour integration across two testing sessions in both healthy and amblyopic adults and children. Zhou et al. (2008) similarly showed that subjects could improve in their ability to discriminate fat and thin interpoled shapes over the course of many trials.

Other studies have also demonstrated top-down influences on PO, which is relevant to the issue of the effects of prior experience on PO. For example, recovery of 3-D shape and contour structure from 2-D line drawings is influenced by higher-level object knowledge (Sinha and Poggio, 1996, 2002). Another demonstration of this point is Dallenbach's (1951) now-classic puzzle-picture, in which perception of the cow is determined partly by the mental set of the observer (see *Figure 1*). Many observers will not see any coherent shape in the image initially, but upon being given appropriate clues, will quickly see the animal's picture emerge. Once subjects see the picture as containing the cow, they cannot help but see the farm animal in all subsequent viewings of the stimulus, indicating that learning PO can sometimes be permanent.



*Figure 1.* Dallenbach's (1951) cow photograph. This is a classic example of how knowledge drives perceptual organization. Once the photograph is seen as a cow (facing towards the viewer), it is virtually always and automatically perceived that way

Priming data also highlight the relevance of past experience to grouping. Early grouping behavior for an impoverished letter stimulus benefits from prior exposure to similar appearing stimuli (Kimchi and Hadad, 2002). Similarly, Zemel et al. (2003) showed that subjects would come to treat severely misaligned, spatially-separated segments as belonging to the same object if those segments were previously shown as being connected. In addition, studies have found ERP evidence for early effects of past experience on figure-ground segregation (Trujillo et al., 2010) and identification of fragmented objects (Viggiano and Kutas, 2000).

Finally, PO, especially earlier kinds, may require certain sorts of experiential input to develop normally. For example, an individual blind from 3.5 years of age was restored sight as a 43-year-old adult and retained only some aspects of visual functioning. He was severely impaired at integrating discrete line segments into a uniform contour, seeing Kanizsa shapes, and segregating overlapping transparent surfaces (Fine et al., 2003). On the other hand, the newly sighted man was not impaired at many higher-level visual functions such as detecting shape from shading, seeing biological motion, and identifying outline shapes. This suggests that some sorts of PO – to be sustained – require experiential input over time.

The foregoing studies imply four conclusions: i) most importantly, PO learning can and does occur; ii) such learning strongly depends on top-down modulation of visual cortex; iii) the majority of performance improvement may develop only after several days, and iv) elements that are best learned in this way are those that group weakly. Because PO itself can primarily be bottom-up (e.g., based on collinearity or correlated orientations – although these linkages may, depending on the nature of the stimulus, need to be augmented by re-entrant processing from later visual and parietal areas, and attention) or be determined by top-down influences (e.g., involving memory and expectations), change in PO dysfunction in schizophrenia may result from a range of bottom-up and top-down factors. In the next section, we re-

view the literature on plasticity of PO in schizophrenia, with the goal of reaching conclusions about which mechanisms are likely to be impaired in this disorder.

### 3. FINDINGS ON SCHIZOPHRENIA

#### *3.1. Schizophrenia and plasticity of perceptual organization*

##### *3.1.1. Within-session learning of PO*

The earliest evidence of reduced learning of PO in schizophrenia comes from Place and Gilmore (1980). These authors showed that when patients and controls attempted to count the number of briefly-presented (i.e., for 20 milliseconds) lines, under three conditions of decreasing line organization, patients performed better than controls in the two most poorly organized conditions and better overall than controls. In this case, intact PO in controls seemed to interfere with line counting in the less organized conditions, whereas patients used the same serial counting strategy in all conditions. However, across the session, there was a trend for controls to improve performance whereas the performance of patients did not benefit from repeated exposure to the stimuli.

Two studies more directly examining within-session training deficits in schizophrenia were performed by Silverstein and colleagues (1998, 2005). Both used a pattern recognition task (PRT), which involved viewing briefly presented (i.e., 100 ms) patterns of 6 asterisks. In Silverstein et al. (1998), there were 360 trials in which a unique pattern was presented. The other 240 trials consisted of quasi-random presentations of a single symmetrical pattern and a single non-symmetrical pattern. The subject's task was to respond, on each trial, whether the currently displayed pattern was "novel" or "repeating" (note – trials were presented in a different random order for each subject, and each subject had a different pair of repeating patterns chosen from the larger stimulus set). This study demonstrated, across 10 trial blocks, that controls improved performance (i.e., correct discrimination between repeating and novel patterns) for both symmetrical and non-symmetrical patterns. In contrast, schizophrenia patients demonstrated a similar learning curve to controls (although at a lower level of absolute performance) for the symmetrical repeating pattern, but did not demonstrate any learning for the non-symmetrical repeating pattern (see *Figure 2*). Moreover, the extent of learning impairment for non-symmetrical patterns was significantly correlated with the level of disorganized symptoms. That is, subjects who were worse at learning the patterns also exhibited more disorganized speech, out-of-context movements, inappropriate affect, etc. This suggests that failure of learning PO was part of a more widespread pattern of cognitive disorganization (Phillips and Silverstein, 2003; see below). Performance was corrected for response bias (i.e., the extent to which a subject indicated he/she had seen a pattern before on the non-repeating trials), but a limitation of this study was that all of the non-repeating (i.e., unique) patterns were non-symmetrical, which may have increased the difficulty discriminating the non-symmetrical repeating pattern from unique stimuli. Therefore, the study was repeated, with different subjects and stimuli, and the 360 non-repeating stimuli were equally balanced between symmetrical and non-symmetrical stimuli (Silverstein et al., 2005). Under these conditions,

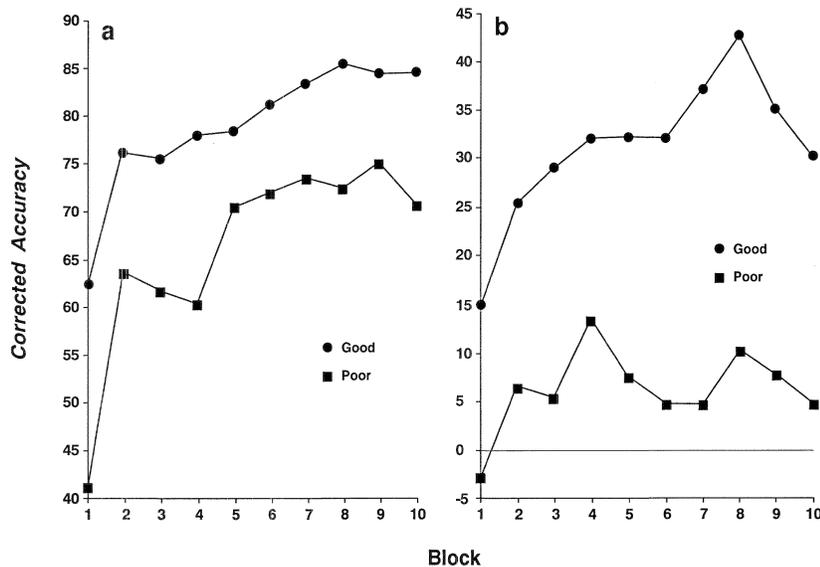
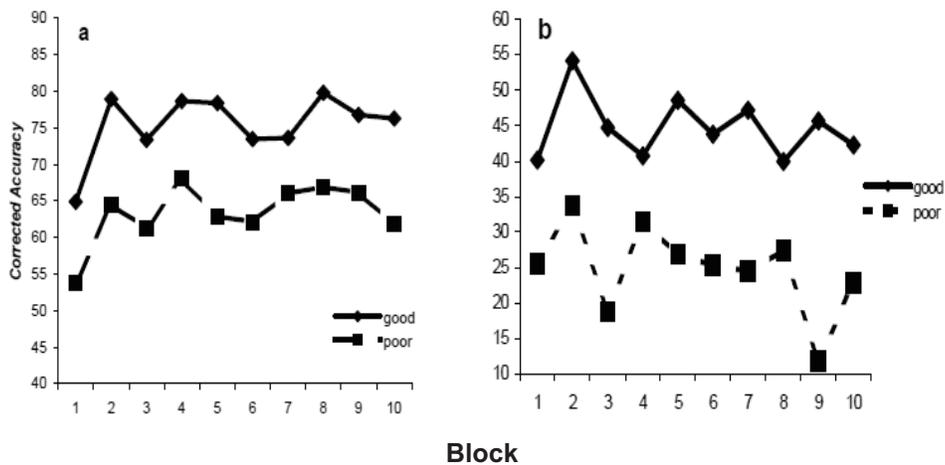


Figure 2. Learning curves from Silverstein et al. (1998). Control subjects demonstrated significant learning (recognition performance) across 10 trial blocks for both symmetrical (good form) and non-symmetrical (poor form) repeating stimuli when these were randomly presented within the context of non-repeating stimuli. In contrast, schizophrenia patients, who performed more poorly overall, demonstrated significant learning only for symmetrical stimuli. Note that in this study, all of the non-repeating stimuli were non-symmetrical

control subjects again demonstrated a significant learning curve in both repeating conditions, but the curves were flatter and performance was lower overall than in the earlier study (see Figure 3, left panel). Among patients, we replicated the main finding of learning only in the symmetrical condition. An important caveat is that the learning effect was far weaker than in the earlier study, and was essentially only observed in Block 2, which was before most of the non-repeating stimuli were presented (see Figure 3, right panel).

What caused closer-to-normal performance in the symmetric condition and more abnormal performance in the asymmetric? Our explanation hinges on the distinction between the admittedly imprecise notions of “top-down” and “bottom-up” processing. Roughly, top-down processing is that which relies on effort, expectations, strategy, learning, memory, intention, utilities, and attention. Bottom-up processing, by contrast, happens automatically in a data-driven fashion with much less regard to factors like expectations, strategy, attention, etc. The usefulness of this distinction for understanding PO is supported by a host of other studies. For example, McMains and Kastner (2011) showed that, first, attention is required to achieve a stable organization when illusory contour formation does not organize the stimulus field into objects; and second, that when bottom-up grouping cues are salient, top-down influence is limited. Marcus and van Essen (2002) similarly showed that top-down influence – in the form of covert attention – can have little effect on individual neurons responding to the boundaries of well-specified illusory shapes, while Gilbert and colleagues showed that more



*Figure 3.* Learning curves from Silverstein et al. (2005), in which half of the non-repeating stimuli were symmetrical and half were non-symmetrical. Control subjects again demonstrated significant learning for both good form and poor form stimuli, but these were flatter than in Silverstein et al. (1998), and performance was lower overall. For schizophrenia patients, they again demonstrated significant improvement only in the symmetrical condition, however, the overall curve was flat except for improvement in Block 2. This suggests that while memory guides perceptual organization better for good than for poor form stimuli, the guidance was weak when discriminations among good form stimuli were required

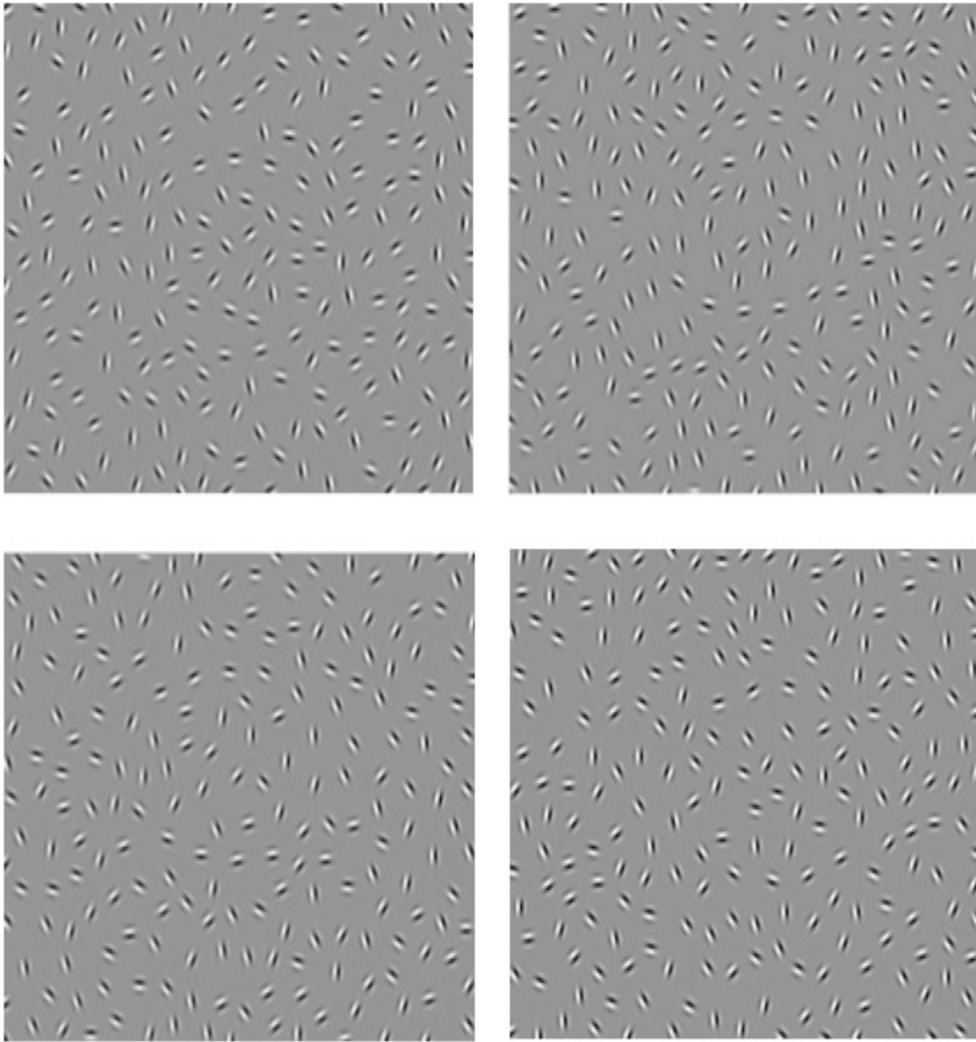
weakly grouping contours elements are strongly subject to top-down (learning) effects (Li, Pièch and Gilbert, 2008). A bird's eye view of these results suggests that top-down factors are strongly relevant to grouping, unless the bottom-up cues are sufficiently salient to preclude such effects.

With this simple top-down, bottom-up distinction in mind, we suggest the behavior exhibited by patients in the laboratory results from reduced top-down influences to PO. Hence, patients learned to detect repeated symmetric patterns somewhat normally because symmetry is detected pre-attentively (for a review, see Wagemans, 1995) and such detection greatly facilitates task performance. Indeed, symmetry perception in schizophrenia has been shown to be intact (Knight et al., 2000). Furthermore, the non-symmetrical patterns were *not* learned by the patients because such erratic structure could only be recovered through a concerted strategy in which structure, so to speak, must be imposed onto the stimulus from top-down mechanisms (e.g., attention, memory, executive control). We realize that this is only a partial picture of the complex mechanisms underlying PRT task performance, but we do think it is an important starting point from which to further understand the differences (and similarities) between patients and matched healthy controls.

A psychophysically rigorous PO task on which patients have demonstrated normal within-session learning with stimuli with strong stimulus-driven cues involves Gabor-defined shape discrimination, sometimes more simply referred to as "contour integration" (Field, Hayes and Hess, 1993; Kovács and Julesz, 1993, 1994). Several variants of the contour integration paradigm have been developed, but all involve detecting or making decisions about a

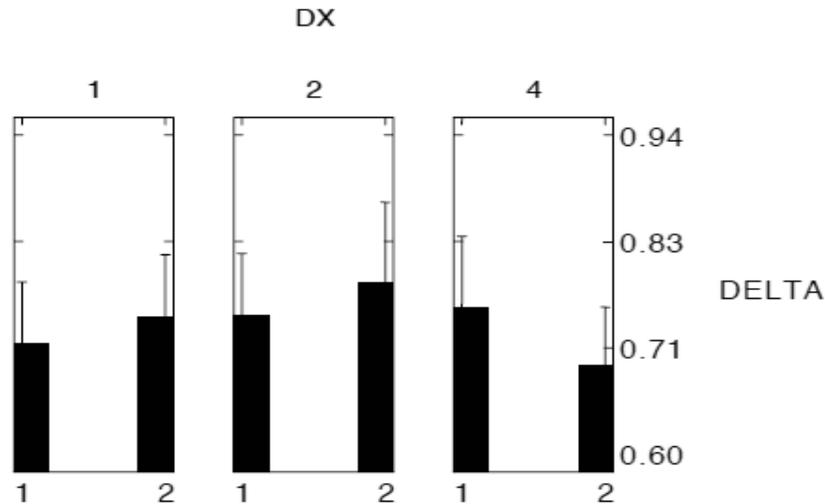
set of Gabor elements embedded in a field of randomly oriented Gabors. In one version, a snake-like path of Gabors must be detected (Field, Hayes and Hess, 1993). This version places relatively greater demands on local grouping mechanisms, and has been used to identify a contour integration deficit in a subgroup of people at high-risk for schizophrenia (Uhlhaas et al., 2004). In another version of the task, subjects must detect and trace a circular contour (Kovács et al., 2000; Pennefather et al. 1999). This version allows for shape-related effects and taps into higher-level organization in addition to local ones. It has also been used to detect contour integration impairment in schizophrenia (Schenkel et al., 2005a; Schenkel, Spaulding and Silverstein, 2005b; Silverstein et al., 2000; Silverstein et al., 2006b; Uhlhaas et al., 2006b; Uhlhaas, Phillips and Silverstein, 2005). In a third version of the task – the one most relevant to this section on within-session learning – subjects must indicate whether a subset of Gabor elements forms a closed shape that tapers either leftward or rightward (see *Figure 4*; Kozma-Wiebe et al., 2006; Silverstein et al., 2009). Task difficulty is manipulated by randomly jittering the orientations of the Gabor elements defining the target shape. Trials are blocked by degree of orientation jitter. A key finding from a recent study (Silverstein et al., in press) was that when the 7° jitter block was presented first in the sequence, performance on that block was 10 percent worse than when the 0° jitter block was presented first. This effect obtained comparably for patients and controls. This can be taken to be a sort of PO priming or *hysteresis* – where prior exposure to strongly grouping configurations can enhance the organization of configurations that tend to group more weakly (Rubin, Nakayama and Shapley, 1997; Anderson, 2007, p. 522; Kellman et al., 2007, p. 505). Since stimuli in the 7° condition still possessed stimulus-driven grouping cues, this finding echoes those from the PRT studies reviewed above in indicating that – despite grouping impairments in schizophrenia – learning in PO can take place when the stimuli contain sufficient bottom-up grouping cues (and when discrimination between multiple similar forms is not required).

An earlier study of the effects of prior exposure on contour integration provides another example of reduced top-down influences on learning of PO. Over four consecutive daily sessions, patients and controls engaged in a task in which they were asked to locate a circular Gabor contour embedded in backgrounds of varying noise density (Silverstein et al., 2006b). On each day of testing, the task was presented under 2 conditions: in increasing order of difficulty (I) and in a random order (R). These two orders were counterbalanced across days and across subjects. A key finding was that, on day 1, controls that received the random-increasing (R-I) sequence had better overall performance (lower detection threshold) than controls that received the I-R sequence. For the schizophrenia group, this pattern did *not* obtain and there was even a non-significant superiority in the I-R condition relative to R-I (see *Figure 5*). The same patterns were observed for both groups on day 2 and so these within-session effects overrode any effects of exposure the prior day, when all subjects received the other sequence (note – sequence effects were absent for both groups on Days 3 and 4). In short, over days 1 and 2, prior exposure, even if in the form of randomly presented stimuli, helped controls when they subsequently viewed the stimuli in a structured (increasing difficulty) order, but patients did not benefit. This paradoxical finding is consistent with the finding that under some conditions, reaction times (RTs) in a simple RT task are longer among people with schizophrenia when the preparatory interval (i.e., the time between the signal that a trial is beginning and the signal to initiate a response) is regular compared to when it is irregular, which



*Figure 4.* Examples of contour integration stimuli. In a recent version of the task, spatially distributed Gabor elements formed a closed egg-shape, and subjects attempted to determine whether the shape pointed left or right (Kozma-Weibe et al., 2006). Top left = right-pointing stimulus with  $0^\circ$  applied to elements of the contour; top right = left-pointing contour with  $\pm 7^\circ$  jitter applied; bottom left = left-pointing contour with  $11^\circ$  jitter applied; bottom right = left-pointing contour with  $15^\circ$  jitter applied. The contour integration paradigm was invented by Field, Hayes and Hess (1993) and further developed by Kovács and Julesz (1993, 1994).

is the opposite of what is observed in other people (reviewed in Nuechterlein, 1977). In both cases, patients demonstrate a reduced sensitivity to information that can help predict the nature, and thereby facilitate processing of, the next stimulus, a form of failure to generate top-down input. Moreover, the data also suggest that regularity, by functioning as an addi-



*Figure 5.* The order  $\times$  group interaction on Day 1 from Silverstein et al. (2006). This graph demonstrates that for nonpatient controls, but not for patient groups, subjects who received the stimuli in a random order (R) first [and the increasing-in-difficulty order (I) second] performed better than subjects who received I first and R second. Specifically, among nonpatients (Dx = 4), the R-I group (Condition 2 on X-axis) had a lower detection threshold (indicating superior performance) than the I-R group (Condition 1 on the X-axis). Note that this same effect was observed on Day 2 (graph not shown), even though the group that received the R-I order on that day had received the opposite order on Day 1 (and showed no performance difference between conditions that day), and that the group that received the I-R order on Day 2 (and showed no performance difference) was the group that had shown the performance difference when they received the R-I order on Day 1. Thus, the order effect overrode a practice effect. Among the schizophrenia (Dx = 1) and schizoaffective (Dx = 2) groups, there was no difference between condition orders on the first two days, indicating a lack of benefit from beginning with an unstructured stimulus sequence and moving to a predictable sequence (thresholds for these two groups were actually nonsignificantly lower in the I-R order condition). On Days 3–4, there were no longer condition order effects for any group. Error bars reflect SD

tional source of information, can impair performance in people with schizophrenia (see also Nuechterlein, 1977 for similar conclusions regarding the RT crossover effect noted above). However, it is important to note that patients benefited from regularity when it was in the form of simple repetition of ideal stimuli (e.g., improving scores with 7° jittered stimuli after prior exposure to a block of 0° jittered stimuli, or learning in the PRT symmetrical condition, as discussed above). Their failure to benefit from regularity only occurred when it was of a more abstract form (e.g., whether the same set of stimuli were being presented in the I-R or R-I order). As is discussed further below, this suggests that, in addition to level of stimulus-driven cues being an important determinant of PO, and PL of PO, in schizophrenia, the degree of concreteness vs. abstraction in the cues from which top-down feedback must be generated is also relevant. Stated differently, patients may be able to use memory to a greater extent than they can use executive functions (e.g., cognitive control, perspective shifting, rule generation) to implement PO. This hypothesis fits with prior data on reduced set shifting to achieve auditory

PO in schizophrenia (Silverstein, Matteson and Knight, 1996), and with much data on impaired executive functioning in the illness (Heinrichs, 2001).

It is unclear as to why patients exhibit approximately normal PO (and PL of PO) for strongly grouping stimuli. Normal performance could occur because top-down factors are less important in these cases or because patients more easily deploy top-down processes when the stimulus already suggests a grouping pattern. Regarding the former, evidence described above suggests that top-down factors are not critical for strongly grouped stimuli, and stimuli from the PRT symmetrical condition and the 0° and 7° jitter conditions in which prior exposure effects in the contour integration task were demonstrated can be classified as such. Evidence against the latter is that patients did not generate top-down input, at least in the same form as controls did, in the condition sequencing study noted above. However, more evidence on this issue is needed before definitive conclusions can be reached. Some further clarification can be found in data examining change in performance over multiple days, a topic to which we now turn.

### 3.1.2. Learning over multiple days

Contour integration performance can improve across multiple days. This was originally demonstrated by Pennefather et al. (1999), who studied change across two days in healthy and amblyopic children and adults. More recently, Gerván and Kovács (2010) demonstrated the importance of consolidation during sleep for these learning effects (which are greater, for example, across 12 hours when sleep occurs between sessions than across an identical temporal interval during the same day). In a study of schizophrenia, Schenkel et al. (2005a) found schizophrenia patients exhibited improvement across three consecutive days on a contour integration task (note – healthy control subjects were not included in this study). In this task, signal-noise ratio (i.e., ratio of the average distance between adjacent background elements relative to the average distance between adjacent contour elements) was decreased systematically with each stimulus, but all embedded Gabor contours were circular (i.e., of “good form”, Garner, 1970) and relatively easy to see at least for the first half of trials. Silverstein et al. (2006b) found that over the course of four days both patients and healthy controls improved significantly on the same task, and the rates of improvement did not differ between groups. It is noteworthy that the Silverstein et al. study gave the test twice each day over *four* days and achieved similar rates of change in patients and controls from first to last testing to that in Schenkel et al. (2005a) where the test was administered to patients once a day for *three* days. Learning improvement was also similar to that of Pennefather et al. (1999) where the test was given to healthy and amblyopic children and adults once for each of *two* days. In all cases, the rate of change varied around a small reduction in threshold (0.05), reflecting an ability to perceive contours at slightly lower signal:noise ratios. These findings are consistent with those of Li and Gilbert (2002) indicating significant change, albeit modest, in contour integration over time, at least prior to six days of training. In short, controls and patients demonstrated similar, but small, degrees of improvement over time on a contour integration task. This is another example of a patient-control similarity in rate of change when a single stimulus type, with “good form” is used (i.e., circular contours).

Recent re-analyses of the data from two of the studies cited above indicate that there were no differences between patient subgroups in amount of performance improvement over time. Schenkel et al. (2005a) examined schizophrenia patients with and without histories of physical and/or sexual abuse (experiences associated with dysregulated hypothalamus-pituitary-adrenal axis activity, chronically elevated cortisol level and cell death and volume reduction in the hippocampus) and found that patients with abuse histories performed more poorly on the task overall; however, there was no difference between the groups in terms of change over time. Silverstein et al. (2006b) examined severely disabled patients who had been in state psychiatric hospitals for many years and compared them to patients who were living in the community or who were about to be discharged after brief hospital stays. Consistent with past findings that abnormal PO predicted longer hospital stays (Silverstein et al., 1998), the long-hospital-stay group performed more poorly overall. However, again, the different groups of schizophrenia patients did not differ on degree of *change* over time (see Figure 6).

The evidence discussed in this section converges with that described in 3.1.1 on within-session learning effects: PL occurred across multiple days among people with schizophrenia for stimuli that were of good form. Because the specific form of multiple-day PL involved an improved ability to perceive fragmented Gabor-defined circular contours against increasingly noisy backgrounds (as opposed to, for example, increased recognition of a single stimulus in the PRT), it is possible that this reflects an increased use of top-down feedback by patients over time, in the form of a greater ability to apply a representation of an intact circular contour (i.e., to achieve a match between this template and incoming visual information). This

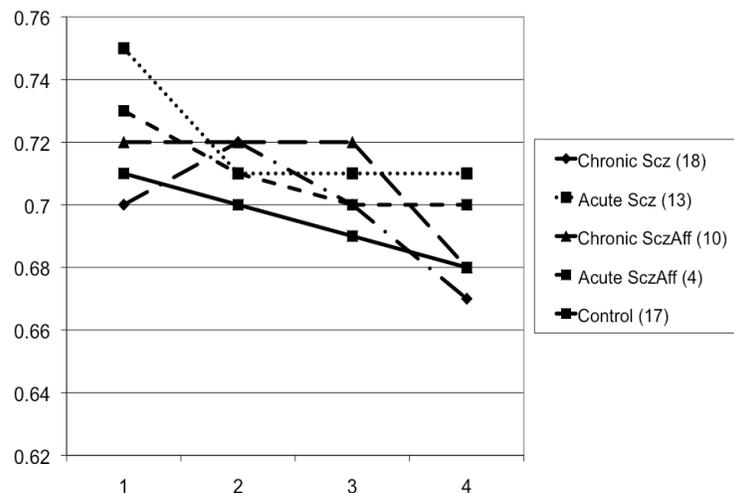


Figure 6. Performance changes in a contour integration performance over 4 days among 5 groups: acute schizophrenia, chronic schizophrenia, acute schizoaffective disorder, chronic schizoaffective disorder, and healthy control groups. Day (1–4) is plotted on the x-axis and Delta is plotted on the y-axis. Delta corresponds to the distance between adjacent target elements divided by the distance between adjacent distractor elements. The main effect of day is significant. The interaction of group  $\times$  day is not significant. These data are from a re-analysis of data originally presented in Silverstein et al. (2006b)

is admittedly speculative, although consistent with Li, Piëch and Gilbert's (2008) finding that more weakly grouping contour elements are most strongly subject to top-down (learning) effects. What makes this case ambiguous is that the basic form of the stimulus (circular) is good, while the signal:noise manipulation reduces its stimulus driven cues to grouping; thus it is somewhat unclear here as to whether to consider top-down influences as operating on strongly or weakly grouped stimuli. Regardless, further studies are needed to clarify the role of top-down factors in improvements in PO of stimuli with strong cues to grouping in people with schizophrenia. Similarly, research is needed on PL for weakly grouped stimuli over multiple days, and on the relative contributions of bottom-up and top-down effects on PO under these conditions.

### *3.2. Effects of treatment on perceptual organization in schizophrenia*

The studies cited above focused on change over 1–4 days, and can thus be viewed as assessing change among subjects whose brain functioning is stable over the (brief) time periods examined. Research has also examined change over time among people undergoing treatment for, and recovery from, acute psychotic episodes, where overall brain functioning is changing significantly between the time points. This research offers a further perspective on plasticity of PO in schizophrenia in that it elucidates the changes in brain activity that underlie PO and perhaps the learning of PO. As an example, Uhlhaas et al. (2005) examined contour integration at two time points: upon admission to an acute-care (i.e., short-term) inpatient unit and then again just prior to hospital discharge, which was typically 23 (SD = 22.2) days later. There were significant subgroup effects. For example, schizophrenia patients with disorganized symptoms demonstrated significant improvement over time in the circular contour detection version of the contour integration task (Silverstein et al., 2000; 2006b). In contrast, stable performance over time was demonstrated by: schizophrenia patients without disorganized symptoms, patients with psychotic symptoms with disorders other than schizophrenia (i.e., bipolar disorder with psychotic features), and non-psychotic psychiatric patients (e.g., with substance abuse or personality disorders). It is important to note here that the disorganized schizophrenia group also performed most poorly at hospital admission and so, essentially, their performance normalized during the course of treatment whereas the other groups' performance remained the same. Interestingly, the magnitude of improvement for the disorganized schizophrenia group was consistent with that of studies of improvement over consecutive days (i.e., a change of 0.05 in signal:noise units for detection threshold), whereas the other groups improved less than in those other studies, presumably due to less consistent experience with the stimuli (i.e., only seeing it twice, 3 weeks apart).

### *3.3. Life experience and perceptual organization*

Schizophrenia patients and people at risk for schizophrenia have demonstrated more veridical perception (compared to controls) of the size of the inner circle in two studies using an Ebbinghaus illusion task (Uhlhaas et al. 2006b; Uhlhaas et al., 2004) (see *Figure 7*). More-

over, in both studies, reduced sensitivity to the illusion (i.e., more accurate size judgments) was related to a greater degree of disorganized symptoms, which was similar to what was found in the contour integration tasks noted above. The Ebbinghaus illusion data are relevant to learning because susceptibility to the illusion appears to require experience with judging perspective in pictures or with internalizing scene statistics (Howe and Purves, 2004). For example, children are less immune to the illusion than adults (Doherty et al., 2010). There are at least two possible explanations for why patients (especially with disorganized symptoms) tend to show a reduced Ebbinghaus illusion effect: 1) they are poor at learning size/distance relationships from an early age (presumably due to a neurodevelopmental abnormality that contributes to the development of schizophrenia); or 2) the illness interferes with the ability to apply the knowledge of these relationships in a top-down fashion when making perceptual judgments. Future studies will need to determine the extent to which each of these two alternatives is correct.

Further evidence that is consistent with reduced learning among schizophrenia patients on the Ebbinghaus task comes from a recent study comparing deaf and hearing schizophrenia pa-

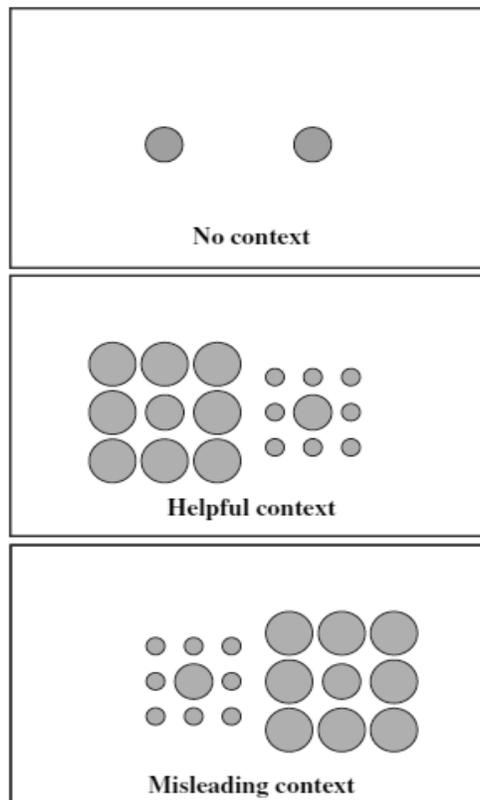


Figure 7. Examples of stimuli from an Ebbinghaus illusion task. On each trial, subjects attempted to determine whether the central circle on the left or right was larger. Control trials (not shown) involved only the central circles

tients (Horton and Silverstein, submitted). In this study, deaf adults with schizophrenia showed the illusion to the same extent as healthy subjects in past studies, whereas hearing patients demonstrated less of an illusion effect (more veridical size judgments), replicating the findings of the two studies discussed above. This finding may be partly explained in terms of attentional differences associated with using sign language. More specifically, mentally healthy deaf people allocate greater attention to peripheral visual stimuli than do hearing people (Dye, Hauser and Bavelier, 2009; Proksch and Bavelier, 2002) and this differential deployment of attention may increase the strength of the illusion (Shulman, 1992) – in this case, overriding the effects of schizophrenia. It is important to note, however, that signing by itself cannot explain the entire effect since some of the cognitive changes associated with deafness are related to cortical reorganization secondary to lack of auditory input (Proksch and Bavelier, 2002). To the extent that some of the effects among deaf schizophrenia patients are due to relying solely on sign language as a means of communicating, however, this is further evidence that experience can reduce the extent of PO impairment in the illness.

Finally, regardless of the explanation for the normal illusion effect in deaf patients, the Ebbinghaus illusion data in hearing schizophrenia patients support the idea – proposed above – that top-down feedback to, and learning of, PO become more impaired as higher-level cognitive factors become more important. For example, the illusion is generated not via a feature binding process such as occurs with contour integration, but secondary to a higher-level cognitive comparison process (Coren, 1971, Coren and Aks, 1990; Coren and Enns, 1993). However, definitive studies need to be done that examine and compare various top-down effects on PL of PO in schizophrenia, ranging from simple prior exposure to those involving regularity of presentation and other more abstract cues.

## 4. CONCLUSIONS

The discussion below will: 1) summarize the computational mechanisms involved in PO modification in schizophrenia; 2) discuss potential biological mechanisms underlying PO plasticity; and 3) outline how these effects fit within our current understanding of plasticity of brain function in healthy and schizophrenia populations.

### 4.1 Computational mechanisms

#### 4.1.1 Perceptual processes

In general, studies of *change* in PO in schizophrenia parallel those studies that did not examine change, in terms of when performance is normal or impaired. Patients demonstrate relatively normal learning of PO when the stimuli possess strong or intermediate cues to grouping, but impaired performance when the stimuli are more novel, weakly grouped, and/or non-symmetrical. In the latter case, grouping must be achieved by imposing organization on the stimulus. Making sense of – and acting optimally on – such forms requires the individual to draw on past experience to form appropriate expectations about the stimuli, to discover the

behavioral significance of patterns therein, and to allocate attentional strategies that make use of the foregoing. These sorts of processes appear to be impaired in schizophrenia.

However, the strength of stimulus-driven grouping is not the only determinant of PO learning; the level of abstraction required to generate top-down feedback also matters. For example, performance with simple, strongly-grouping stimuli improves after repeated exposure, but similar improvement is not found when the only task-related cues are less concrete (e.g., whether stimuli are presented in increasingly more or increasingly less structured orders).

An unresolved issue is the extent to which reduced top-down feedback to PO in schizophrenia is secondary to inadequate perceptual grouping. In other words, bottom-up failures in element linking may preclude formation of a representation of a perceptual group in the first place, which would then preclude learning of such a representation. We believe that some findings of top-down processing failures in PO learning in schizophrenia can be explained in this way, especially given consistent findings of poorer overall performance even on simple contour integration tasks (e.g., Silverstein et al., 2000, 2009), and evidence that basic contour linking is impaired (Kéri et al., 2005; Must et al., 2004) even when attention is normal (Keri et al. 2009; cf. Freeman and Driver, 2005; Freeman, Sagi and Driver, 2001, 2004; Freeman et al., 2003 for evidence on the role of attention in contour linking). This evidence suggests basic bottom-up failures of PO in schizophrenia. However, evidence does exist also for a relatively “pure” failure of top-down input; in Silverstein et al. (2006b), acute (but not chronic) schizophrenia patients demonstrated normal contour integration and even the same degree of improvement over 4 days as controls suggesting an intact ability to organize the stimuli, but both patient groups were still insensitive to the effects of random versus sequential stimulus presentation on contour integration within single sessions. This finding that task performance for the same stimuli is intact in certain contexts but impaired in others strongly suggests a failure of top-down influence on PO. Therefore, we conclude that there are multiple contributors to impaired PL of PO in schizophrenia, and *that these are the same factors responsible for the PO impairment in general*, namely: 1) a weakening of bottom-up feature binding, which can lead to reduced transient attention to the contour, and reduced quality of re-entrant activity from parietal and frontal areas to visual cortex (cf. Bouvier and Treisman, 2010); 2) and reduced top-down feedback in the form of reduced sensitivity to task context, including stimulus presentation and environmental regularities.

Importantly, we do not see reduced PO and PL of PO as due to the general effort-related, *sustained* attentional disturbance in schizophrenia (see Heinrichs and Zakzanis, 1998; Heinrichs, 2001; Nuechterlein, 1977 for reviews). This is because: a) in cases where stimulus grouping would interfere with task performance, patients perform better than controls overall; b) patients demonstrate normal PL of PO when there are stronger cues to grouping; and c) patients and controls benefit similarly on contour integration tasks from prior exposure to ideal stimulus exemplars – all of which are inconsistent with a general sustained attention deficit explanation of PO impairments in the illness. Rather, in our view, it is a specific aspect of feedback or gain control, likely related to attention albeit in an admittedly imprecise way at this point, that is involved in PO disturbances in schizophrenia: this being that weaker PO for forms with few stimulus-driven cues to grouping causes a reduction in grouping-initiated feedback (from temporal, parietal and frontal areas) to maintain and enhance the salience of

the emergent perceptual group. This is consistent with neuropsychological data suggesting that: a) activation within the temporo-parietal junction is necessary for target-noise segregation when global perception cannot be achieved via local cortico-cortical interactions (Piccini et al., 2003); and b) the prefrontal cortex is necessary to maintain a representation of visual stimuli in extrastriate visual areas (Barcelò, Suwazono and Knight, 2000; Windmann et al., 2006). A remaining issue for future research is the extent to which there are conditions under which PO, and consequently PL of PO, impairments in schizophrenia are due purely to bottom-up factors. Regarding this, it should be noted that while that PO without attention can occur for extremely simple input (Razpurker-Apfelt and Pratt, 2008), schizophrenia patients have thus far demonstrated normal performance with similar stimuli (Carr, Dewis and Lewin, 1998; Cox and Leventhal, 1978), although this has not yet been demonstrated in a PL context. Importantly, it will also be useful to refine our concepts of top-down and bottom-up processing as it relates to PO, and to clarify how less effortful and more effortful forms of attention fit within these processes.

Finally, recent models of PL highlight the role of top-down mechanisms modulating visual cortex responses by reweighting specific representations in decision or response units (Doshier and Lu, 2009), retuning read-out signals (as opposed to changing the way stimuli are encoded) (Kourtzi, 2009), or learning an algorithm wherein an ideal output is associated with specific patterns of input (Sinha and Poggio, 2002). Evidence of impaired learning, decision making and response preparation in schizophrenia (e.g., Heerey, Bell-Warren and Gold, 2008), including during PO tasks (e.g., Silverstein et al., 2010b) indirectly suggests that these hypothesized processes are impaired in the learning of PO.

## 4.2 Neurobiological mechanisms

### 4.2.1 Excitation and inhibition

Recent models of PL highlight both stimulus enhancement and (external) noise exclusion mechanisms (Lu and Doshier, 2009) and this corroborates findings that both inhibitory and excitatory processes can be affected by practice (Zenger and Sagi, 2002). To date, however, while evidence for both reduced excitatory and inhibitory activity has been found in schizophrenia, the extent to which each contributes to PO, and PL of PO, in the illness is either ambiguous or lacking. For example, there is evidence for reduced synchrony during PO tasks among schizophrenia patients (Uhlhaas et al., 2006a) but this result can be explained in a number of different ways: a) reduced excitatory activity, in the form of NMDA-receptor hypofunction, limiting the formation of long-range horizontal connectivity between pyramidal cells in visual cortex; b) reduced GABA-ergic (inhibitory) interneuron activity limiting the extent of possible noise exclusion; c) reduced interneuron activity secondary to reduced excitatory input onto them from pyramidal cells; and/or d) reduced acetylcholine release, which serves as a setting condition for NMDA-receptor functioning (Friston, 2005; Uhlhaas and Singer, 2006; Uhlhaas et al., 2009). The data do not uniquely support one of these alternatives over the other at this point.

Moreover only a small number of perception studies have provided direct data on reduced inhibition and excitation in schizophrenia. For example, in the contrast-contrast effect (Chubb, Sperling and Solomon, 1989), for a given spatial frequency band, subjects tend to misjudge the contrast of a patch of blurred luminance noise when it is surrounded by noise of a different contrast. The explanation is that the responses of spatial-frequency tuned neurons to the central patch are normalized (inhibited) by similarly-tuned, nearby neurons responding to the surround. Such inhibition is reduced in patients (Dakin, Carlin and Hemsley, 2005), at least if they are lower-functioning (Silverstein et al., 2010a). In a related study, patients were less affected by orientation in the surround when judging the contrast of an oriented luminance grating. This result was attributed to reduced surround inhibition, secondary to a reduction in GABA (an inhibitory neurotransmitter) concentration in visual cortex, as measured by magnetic resonance spectroscopy (Yoon et al., 2010).

#### 4.2.2 Altered neurotransmitter activity

In our view, one of the more plausible theories of cognitive/perceptual dysfunction in schizophrenia implicates hypofunction of NMDA glutamatergic receptors; these receptors are normally associated with excitatory connectivity and the formation of neuronal networks such as those involved in implementing PO. In the next two paragraphs, we summarize the evidence for this theory and discuss its relevance for understanding PL of PO in schizophrenia.

As noted above, the degree of improvement in PO was significantly correlated with a reduction in disorganized, but not positive or negative symptoms. The strong link between 'perceptual disorganization' and clinical disorganization supports multiple studies by various research groups linking PO deficits and disorganized symptoms in cross-sectional investigations (reviewed in Uhlhaas and Silverstein, 2005; see also Uhlhaas et al., 2006b). Silverstein and Schenkel (1997) and Phillips and Silverstein (2003) proposed that all of these forms of reduced cognitive organization (i.e., fragmentation in perception, thinking, motor activity, and affective output) have their basis in reduced contextual modulation of cognitive activity. This is thought to lead to a predominance of feedforward activity relative to contextually modulated, or higher-order, representations, such as those normally generated by PO, selective attention, lexical disambiguation, and abstract reasoning. Moreover, these authors proposed that these multiple forms of disorganization in schizophrenia reflect hypoactivity of NMDA-receptor functioning and perhaps also reduced inhibitory activity of parvalbumin-containing GABA-ergic interneurons (secondary to reduced NMDA-mediated excitatory input onto interneurons) (see Roopun et al., 2008; Spencer, 2009; and Uhlhaas et al., 2008 for reviews). Several lines of evidence point to NMDA receptor hypofunction in schizophrenia (Olney, Newcomer and Farber, 1999), and this abnormality is considered a major contributor to reduced synchrony of beta- and gamma-band oscillations in schizophrenia (reviewed in Lisman et al., 2008; Uhlhaas and Singer, 2006; Uhlhaas et al., 2009), which, in turn, are associated with reduced PO in this illness (Spencer et al., 2003, 2004; Uhlhaas et al., 2006a). This view is supported by the known links between PO and synchrony in healthy humans and animals (Phillips and Singer, 1997; Singer, 1995). Indirect evidence for the role of NMDA receptor hypofunction in PO impairments in schizophrenia comes from a study by Uhlhaas et al.

(2007) on the effects of ketamine on contour integration in non-psychiatrically ill adults. Ketamine is a drug that produces psychotic symptoms and that blocks activity at NMDA receptors. Uhlhaas et al. (2007) demonstrated that on the night of ketamine use, users were impaired on contour integration, whereas after three days of non-use, performance improved to within the normal range. The implication of all of this evidence is that treatment-related improvement in PO – along with treatment-related reduction in disorganized symptoms (Uhlhaas et al., 2005) – is due to an increased ability of patients to integrate information in a context-driven fashion, in multiple perceptual and cognitive domains.

The view of NMDA receptor hypofunction as the biological basis for PO impairment in schizophrenia is also relevant to PL of PO because NMDA receptor activity has been implicated in both fast-acting plasticity (e.g., that can support PO), as well as longer-term changes including long term potentiation (LTP) and learning effects (Kay and Phillips, in press; Phillips and Singer, 1997). The multiple roles of NMDA receptor activity in perception and learning, which take place at very different time scales, may be a function of the subclass of NMDA receptor involved in each process (Cull-Candy and Leszkiewicz, 2004; Kay and Phillips, in press; Phillips and Singer, 1997; Yashiro and Philpot, 2008). A common basis for PO, and PL of PO, in schizophrenia could account for why patients appear to be most impaired in both domains under the same conditions: when factors beyond stimulus-driven cues to grouping are required for PO. It is important to note here that findings that patients can group and learn to group visual stimuli under some conditions indicates that the modulatory activity provided by NMDA receptors is weakened, but not absent.

#### 4.2.3 Sleep

The normal rate of change over time on some PO tasks argues against failures of sleep-dependent learning mechanisms in schizophrenia. The pattern of change vs. no-change over time on PO tasks in schizophrenia appears to most simply be explained in terms of stimulus and task factors (e.g., grouping strength) as noted above. A notable counterexample may be motor learning impairments (Manoach et al., 2004). However, since motor learning was found to be intact within-session but impaired across days – which is the opposite of the PO change data reported here – data on motor and PL in schizophrenia may not be directly comparable.

#### 4.2.4 Treatment implications

The findings on PO plasticity in schizophrenia have implications for pharmacologic treatment. As noted above, acetylcholine is important for PL (Friston, 2005), especially in: enhancing communication between early and late visual mechanisms (Herzog and Fahle, 2002); mediating NMDA receptor plasticity (Gu, 2002; Sabatino et al., 1999); and enhancing GABA-mediated synchrony (Maggi, Sher and Cherubini, 2001). It has also recently been demonstrated that acetylcholine release facilitates long-term enhancement of visual evoked potential amplitude in rat V1 (Kang and Vaucher, 2009). This is relevant to schizophrenia be-

cause many medications used to treat psychotic symptoms, as well as medications used to treat the side effects of antipsychotic medication, block acetylcholine receptors. These have been shown to significantly impair attention, declarative memory and visual memory in the disorder (Minzenberg et al., 2004), thereby potentially limiting PL in schizophrenia. *A key implication of these data is that medications with minimal anticholinergic load will allow for greater PL.* It is also possible, although untested to date, that medications that enhance cholinergic activity may facilitate PL by enhancing excitatory (NMDA-related) and inhibitory (GABA-ergic) mechanisms. Such indirect approaches to PL are important because, for example, direct stimulation of NMDA receptors is not possible, due to the high potential for neurotoxicity and cell death. Moreover, effective modulators of GABA activity that target cognition have not yet been created – other than tobacco, which acts on nicotinic acetylcholine receptors to increase the output of inhibitory interneurons (Lisman et al., 2008). The effect of nicotine may perhaps explain its widespread use (>80%) and cognitive enhancing effects in schizophrenia (Leonard, Mexal and Freedman, 2007) as well as in the general population. Finally, it should be noted that while the specific relationship between anticholinergic load, PO, and PL of PO, in schizophrenia needs to be investigated, and that this is a potential confound in many past studies since smoking patterns and recent nicotine use are not typically assessed, it could not explain all past findings on PO in schizophrenia since: a) some studies have used unmedicated patients; b) independence of overall medication dose and task performance argues against a significant role of the anticholinergic component, although it is possible this was obscured by differences in this component in different medications across patients; and c) in several studies, level of PO was clearly a function of patient subtype (i.e., disorganized or not) yet all patient subgroups were taking antipsychotic medications. This last point suggests that illness-related factors play a greater role than medication-related factors in determining PO and PL of PO performance.

#### 4.2.5. Developmental implications

An important question is how PO and its associated PL impairment develop in schizophrenia. It is known that the development of ventral visual cortex extends through adolescence (Golarai et al., 2010), which is when the prodromal or acute stages of schizophrenia often begin. There are also developmental changes in GABA-ergic mechanisms in visual cortex across the lifespan (Pinto et al., 2010), and in the expression of NMDA receptor subtypes (Yashiro and Philpot, 2008). These data suggest that the development of schizophrenia interrupts the normal development of brain regions involved in PO, as well as the neurotransmitter systems thought to subservise PO. Since this would occur after much development has already taken place, it is consistent with findings that PO for stimuli with strong grouping potential, which rely on PO mechanisms that are intact at birth or shortly thereafter, is more intact than PO of more novel patterns, where greater top-down input and other later developing mechanisms are required. This is also consistent with the often-demonstrated impairments in prefrontal cortex – a structure that does not develop fully until late adolescence – functioning in schizophrenia (Heinrichs, 2001). Others have also shown that primary sensory regions develop first, followed by the parietal and then frontal areas (Gogtay et al., 2004). This course of

development, again, suggests that ontogenetically later areas should be those most susceptible to the onset of schizophrenia. It also fits the suggestion that top-down feedback to PO in schizophrenia is weakest when it is based on more abstract cues (e.g., stimulus ordering) or on an active cognitive comparison process (e.g., with the Ebbinghaus illusion) – both of which would involve the prefrontal cortex – compared to when top-down feedback can be generated by memory traces generated via repeated exposure.

Finally, alterations in PO, and PL of PO, may be related to illness-related changes in the expression of genes that support neurotransmitter function and plasticity. Recent years have seen increased understanding of: a) the genetics of NMDA receptor hypofunction in schizophrenia and its link to generating synchronized oscillations (Lisman et al., 2008); b) developmental changes in synchrony across childhood and adolescence and their link to myelination and the development of GABA transmission (Uhlhaas et al., 2010); and c) adolescent changes in the molecular (i.e., gene expression) mechanisms that are critical for a number of aspects of adolescent development that are disturbed in schizophrenia, including glutamatergic activity and plasticity (Harris et al., 2009). Further specification of the genetics underlying network dysfunction will clarify the biological basis of PO and PO learning impairments in schizophrenia; it will also yield insights into how these processes are implemented in the healthy brain.

#### *4.3 Implications for understanding plasticity and its impairment in schizophrenia*

The data reviewed above on contour integration in schizophrenia indicate *normal*, multiple-day, practice-related change within the context of *impaired* PO at baseline. While this may appear paradoxical if both PO and PL are assumed to be based in the same process, recent work on plasticity can shed light on the meaning of this pattern. For example, Gilbert, Li and Piech (2009) noted that PL involves both long-term modification of cortical circuits, as well as adaptive changes in the short term dynamics of the functional properties of cortical neurons. Regarding the latter, Gilbert et al. noted that they can be affected by top-down influences such as attention, expectations and task demands (perhaps via attention). On this view, the data reviewed above can be interpreted as suggesting that schizophrenia may be characterized by a relatively more severe impairment in short-term plasticity (especially when top-down input is required to implement it) such as that involved in implementing PO over the first 300 milliseconds of processing, and a relatively less severe impairment in long-term neuronal modification, such as that involved in PL over the course of days and involving sleep-related mechanisms. Such a view was proposed, on the basis of different evidence, by Peled (2004), who conceptualized psychotic disorders (including, and prototypically, schizophrenia) as a disturbance of neural complexity (i.e., neural network integration) resulting in altered fast stabilizing plasticity (but not in slower-developing plasticity). This view is also consistent with evidence from plasticity-based approaches to cognitive rehabilitation in schizophrenia, which demonstrate impairments in perceptual processing at baseline, but then improvements over time with training (Fisher et al., 2009). Moreover, this view fits with data from long-term behavioral rehabilitation that demonstrate significant learning of complex behaviors in intensive

inpatient social-learning environments despite severe deficits in these behaviors upon program admission (e.g., Corrigan and Liberman, 1994; Paul and Lentz, 1977; Silverstein et al., 2006a). In short, the views of Gilbert et al. (2009) and Peled (2004) can potentially clarify why people with schizophrenia demonstrate more PO impairments under conditions when top-down input is critical for grouping, why PL of PO is most affected when top-down input is required to facilitate grouping, and why performance change over multiple days is equivalent to that of control subjects. Conversely, the data on schizophrenia provide confirmatory evidence for the separability of short-term and long-term plasticity processes in general. An important caveat is necessary here, however. This is that while forms of plasticity may be relatively independent in a healthy population, it is clear that in schizophrenia, for weakly grouped stimuli (such as the nonsymmetrical stimuli used in the PRT), reduced PO at baseline is a rate-limiting factor for the development of PL within a single session (and possibly over multiple days as well, although this is yet to be investigated). Therefore, while the potential for PO to be modified (i.e., slow plasticity) appears to be greater than the ability to initially achieve PO (i.e., fast plasticity), this may only obtain for stimuli with relatively more stimulus-driven cues to grouping, and there may be a form quality threshold beyond which severity of initial PO impairment precludes significant single session and multiple-day learning.

## REFERENCES

- Ahissar, M. (1999): Perceptual learning. *Current Directions in Psychological Science*, 8, 124–128.
- Ahissar, M., Hochstein, S. (1996): Learning pop-out detection: Specificities to stimulus characteristics. *Vision Research*, 36, 3487–3500.
- Ahissar, M., Laiwand, R., Kozminsky, G., Hochstein, S. (1998): Learning pop-out detection: Building representations for conflicting target-distractor relationships. *Vision Research*, 38, 3095–3107.
- Altmann, C. F., Bühlhoff, H. H., Kourtzi, Z. (2003): Perceptual organization of local elements into global shapes in the human visual cortex. *Current Biology*, 13, 342–349.
- American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition. 1994. Washington, DC: Author.
- Anderson, B. L. (2007): Filling-in theories of completion: Rejoinder to Kellman, Garrigan, Shipley, and Keane (2007) and Albert (2007). *Psychological Review*, 114(2), 509–527.
- Barcelò, F., Suwazono, S., Knight, R. T. (2000): Prefrontal modulation of visual processing in humans. *Nature Neuroscience*, 3, 399–403.
- Bouvier, S., Treisman, A. (2010): Visual feature binding requires reentry. *Psychological Science*, 21, 200–204.
- Brady, M. J., Kersten, D. (2003): Bootstrapped learning of novel objects. *Journal of Vision*, 3, 413–422.
- Büchel, C., Coull, J. T., Friston, K. J. (1999): The predictive value of changes in effective connectivity for human learning. *Science*, 283, 1538–1541.
- Butler, P. D., Silverstein, S. M., Dakin, S. C. (2008): Visual perception and its impairment in schizophrenia. *Biological Psychiatry*, 64, 40–47.
- Carr, V. J., Dewis, S. A., Lewin, T. J. (1998): Preattentive visual search and perceptual grouping in schizophrenia. *Psychiatry Research*, 79, 151–162.
- Chapman, J. (1966): The early stages of schizophrenia. *British Journal of Psychiatry*, 112, 225–251.
- Chubb, C., Sperling, G., Solomon, J. A. (1989): Texture interactions determine perceived contrast. *Proceedings of the National Academy of Sciences U S A*, 86, 9631–9635.

- Ciaramelli, E., Leo, F., Del Viva, M. M., Burr, D. C., Ladavas, E. (2007): The contribution of prefrontal cortex to global perception. *Experimental Brain Research*, *181*, 427–434.
- Coren, S. (1971): A size contrast illusion without physical size difference. *American Journal of Psychology*, *84*, 565–566.
- Coren, S., Aks, D. J. (1990): Moon illusion in pictures: A multi-mechanism approach. *Journal of Experimental Psychology: Human Perception and Performance*, *16*, 365–380.
- Coren, S., Enns, J. T. (1993): Size contrast as a function of conceptual similarity between test and inducers. *Perception and Psychophysics*, *54*, 579–588.
- Corrigan, P. W., Liberman R. P. (eds) (1994): *Behavior Therapy in Psychiatric Hospitals*. New York: Springer.
- Cox, M. D., Leventhal, D. B. (1978): A multivariate analysis and modification of a preattentive, perceptual dysfunction in schizophrenia. *Journal of Nervous and Mental Disease*, *166*, 709–718.
- Cull-Candy, S. G., Leszkiewicz, D. N. (2004): Role of distinct NMDA receptor subtypes at central synapses. Science’s STKE: Signal Transduction Knowledge Environment, 2004(255), re16.
- Dakin, S., Carlin, P., Hemsley, D. (2005): Weak suppression of visual context in chronic schizophrenia. *Current Biology*, *15*, 822–824.
- Dallenbach, K. M. (1951): A puzzle-picture with a new principle of concealment. *American Journal of Psychology*, *64*, 431–433.
- Doherty, M. J., Campbell, N. M., Tsuji, H., Phillips, W. A. (2010): The Ebbinghaus illusion deceives adults but not young children. *Developmental Science*, *13*, 714–721.
- Doshier, B. A., Lu, Z-L. (1999): Mechanisms of perceptual learning. *Vision Research*, *39*, 31970–3221.
- Doshier, B. A., Lu, Z-L. (2009): Hebbian reweighting on stable representations in perceptual learning. *Learning and Perception*, *1*, 37–58.
- Dye, M. W., Hauser, P. C., Bavelier, D. (2009): Is visual selective attention in deaf individuals enhanced or deficient? The case of the useful field of view. *PLoS One*, *4*(5), e5640.
- Erickson, C. A., Jagadeesh, B., Desimone, R. (2000): Clustering of perirhinal neurons with similar properties following visual experience in adult monkeys. *Nature Neuroscience*, *3*, 1143–1148.
- Field, D. J., Hayes, A., Hess, R. F. (1993): Contour integration by the human visual system: Evidence for a local “association field”. *Vision Research*, *33*, 173–193.
- Fine, I., Jacobs, R. A. (2000): Perceptual learning for a pattern discrimination task. *Vision Research*, *40*, 3209–3230.
- Fine, I., Wade, A. R., Brewer, A. A., May, M. G., Goodman, D. F., Boynton, G. M., Wandell, B. A., MacLeod, D. I. (2003): Long-term deprivation affects visual perception and cortex. *Nature Neuroscience*, *6*, 915–916.
- Fisher, M., Holland, C., Merzenich, M. M., Vinogradov, S. (2009): Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *American Journal of Psychiatry*, *166*, 805–811.
- Freeman, E., Driver, J. (2005): Task-dependent modulation of target-flanker lateral interactions in vision. *Perception and Psychophysics*, *67*, 624–637.
- Freeman, E., Sagi, D., Driver, J. (2001): Lateral interactions between targets and flankers in low-level vision depend on attention to the flankers. *Nature Neuroscience*, *4*, 1032–1036.
- Freeman, E., Sagi, D., Driver, J. (2004): Configuration-specific attentional modulation of flanker-target lateral interactions. *Perception*, *33*, 181–194.
- Freeman, E., Driver, J., Sagi, D., Zhaoping, L. (2003): Top-down modulation of lateral interactions in early vision: Does attention affect integration of the whole or just perception of the parts? *Current Biology*, *13*, 985–989.
- Friston, K. (2005): Disconnection and cognitive dysmetria in schizophrenia. *American Journal of Psychiatry*, *162*, 429–432.

- Furmanski, C. S., Engel, S. A. (2000): Perceptual learning in object recognition: Object specificity and size invariance. *Vision Research*, 40, 474–484.
- Fuster, J. M. (2005): *Cortex and Mind: Unifying Cognition*. New York: Oxford University Press, USA.
- Garner, W. R. (1970): Good patterns have few alternatives. *American Scientist*, 58, 34–42.
- Gerván, P., Kovács, I. (2010): Two phases of offline learning in contour integration. *Journal of Vision*, 10, 24. doi: 10.1167/10.6.24
- Gilbert, C. D., Li, W., Piech, V. (2009): Perceptual learning and adult cortical plasticity. *Journal of Physiology*, 587, 2743–2751.
- Gilbert, C. D., Sigman, M., Crist, R. E. (2001): The neural basis of perceptual learning. *Neuron*, 31, 681–697.
- Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., Nugent, T. F. III, Herman, D. H., Clasen, L. S., Toga, A. W., Rapoport, J. L., Thompson, P. M. (2004): Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences, USA*, 101, 8174–8179.
- Golarai, G., Liberman, A., Yoon, J. M., Grill-Spector, K. (2010): Differential development of the ventral visual cortex extends through adolescence. *Frontiers in Human Neuroscience*, 3, 80.
- Gu, Q. (2002): Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. *Neuroscience*, 111, 815–835.
- Harris, L. W., Lockstone, H. E., Khaitovich, P., Weickert, C. S., Webster, M. J., Bahn, S. (2009): Gene expression in the prefrontal cortex during adolescence: Implications for the onset of schizophrenia. *BMC Medical Genomics*, 2, 28. doi:10.1186/1755-8794-2-28.
- Heerey, E. A., Bell-Warren, K. R., Gold, J. M. (2008): Decision-making impairments in the context of intact reward sensitivity in schizophrenia. *Biological Psychiatry*, 64, 62–69.
- Heinrichs, R. W. (2001): *In Search of Madness*. New York: Oxford University Press.
- Heinrichs, R. W., Zakzanis, K. K. (1998): Neurocognitive deficit in schizophrenia. A quantitative review of the evidence. *Neuropsychology*, 12, 426–445.
- Hemsley, D. R. (1994): Perceptual and cognitive abnormalities as the bases for schizophrenic symptoms. In David, A. S., Cutting, J. (eds), *The Neuropsychology of Schizophrenia*. Hove, UK: Psychology Press, pp. 97–116.
- Herzog, M. H., Fahle, M. (2002): Top-down information and models of perceptual learning. In Fahle, M., Poggio, T. (eds), *Perceptual Learning*. Cambridge, MA: MIT Press, pp. 367–378.
- Horton, H., Silverstein, S. M. The Ebbinghaus illusion in deaf versus hearing people with schizophrenia. (Manuscript submitted for publication.)
- Howe, C. Q., Purves, D. (2004): Size contrast and assimilation explained by the statistics of natural scene geometry. *Journal of Cognitive Neuroscience*, 16, 90–102.
- Jagadeesh, B., Chelazzi, L., Mishkin, M., Desimone, R. (2001): Learning increases stimulus salience in anterior inferior temporal cortex of the macaque. *Journal of Neurophysiology*, 86, 290–303.
- Kang, J. I., Vaucher, E. (2009): Cholinergic pairing with visual activation results in long-term enhancement of visual evoked potentials. *PLoS One*, 4(6), e5995.
- Karni, A., Sagi, D. (1991): Where practice makes perfect in texture discrimination: Evidence for primary visual cortex plasticity. *Proceedings of the National Academy of Sciences U S A*, 88, 4966–4970.
- Karni, A., Sagi, D. (1993): The time course of learning a visual skill. *Nature*, 365, 250–252.
- Karni, A., Tanne, D., Rubenstein, B. S., Askenasy, J. J., Sagi, D. (1994): Dependence on REM sleep of overnight improvement of a perceptual skill. *Science*, 265, 679–682.
- Kay, J. W., Phillips, W. A.: Coherent infomax as a computational goal for neural systems. *Bulletin of Mathematical Biology*. (In press).

- Kellman, P. J., Garrigan, P., Shipley, T. F., Keane, B. P. (2007): Interpolation processes in object perception: Reply to Anderson (2007). *Psychological Review*, 114(2), 488–508.
- Kéri, S., Kelemen, O., Benedek, G. (2009): Attentional modulation of perceptual organisation in schizophrenia. *Cognitive Neuropsychiatry*, 14, 77–86.
- Kéri, S., Kelemen, O., Benedek, G., Janka, Z. (2005): Lateral interactions in the visual cortex of patients with schizophrenia and bipolar disorder. *Psychological Medicine*, 35, 1043–1051.
- Kimchi, R., Hadad, B. S. (2002): Influence of past experience on perceptual grouping. *Psychological Science*, 13, 41–47.
- Knight, R. A., Manoach, D. S., Elliott, D. S., Hershenson, M. (2000): Perceptual organization in schizophrenia: The processing of symmetrical configurations. *Journal of Abnormal Psychology*, 109, 575–587.
- Kourtzi, Z. (2009): Visual learning for flexible decisions in the human brain. *Learning and Perception*, 1, 99–114.
- Kourtzi, Z., Tolias, A. S., Altmann, C. F., Augath, M., Logothetis, N. K. (2003): Integration of local features into global shapes: Monkey and human fMRI studies. *Neuron*, 37, 333–346.
- Kovács, I. (2000): Human development of perceptual organization. *Vision Research*, 40, 1301–1310.
- Kovács, I., Julesz, B. (1993): A closed curve is much more than an incomplete one: Effect of closure in figure-ground segmentation. *Proceedings of the National Academy of Sciences USA*, 90, 7495–7497.
- Kovács I., Julesz, B. (1994): Perceptual sensitivity maps within globally defined visual shapes. *Nature*, 370, 644–646.
- Kovács, I., Kozma, P., Fehér, A., Benedek, G. (1999): Late maturation of visual spatial integration in humans. *Proceedings of the National Academy of Sciences, U S A*, 96, 12204–12209.
- Kovács, I., Polat, U., Pennefather, P. M., Chandna, A., Norcia, A. M. (2000): A new test of contour integration deficits in patients with a history of disrupted binocular experience during visual development. *Vision Research*, 40, 1775–1783.
- Kozma-Wiebe, P., Silverstein, S., Fehér, Á., Kovács, I., Uhlhaas, P., Wilkniss, S. (2006): Development of a World-Wide Web based contour integration test: Reliability and validity. *Computers in Human Behavior*, 22, 971–980.
- Laurent, G. (2010): Sequence coding and learning. In Singer, W., Malsburg, C. V. D., Phillips, W. A. (eds), *Dynamic Coordination in the Brain: From Molecules to Mind: Ernst Strüngmann Forum Report #5*. Cambridge, MA: MIT Press, pp. 35–42.
- Leonard, S., Mexal, S., Freedman R. (2007): Smoking, genetics and schizophrenia: Evidence for self medication. *Journal of Dual Diagnosis*, 3, 43–59.
- Li, W., Gilbert, C. D. (2002): Global contour saliency and local colinear interactions. *Journal of Neurophysiology*, 88, 2846–2856.
- Li, W., Piëch, V., Gilbert, C. D. (2008): Learning to link visual contours. *Neuron*, 57, 442–451.
- Lisman, J. E., Coyle, J. T., Green, R. W., Javitt, D. C., Benes, F. M., Heckers, S., Grace, A. A. (2008): Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends in Neurosciences*, 31, 234–242.
- Löwel, S., Singer, W. (2002): Experience-dependent plasticity of intracortical connections. In Fahle, M., Poggio, T. (eds), *Perceptual Learning*. Cambridge, MA: MIT Press, pp. 3–18.
- Lu, Z-L., Doshier, B. A. (2009): Mechanisms of perceptual learning. *Learning and Perception*, 1, 19–36.
- Maggi, L., Sher, E., Cherubini, E. (2001): Regulation of GABA release by nicotinic acetylcholine receptors in the neonatal rat hippocampus. *Journal of Physiology*, 536, 89–100.

- Manoach, D. S., Cain, M. S., Vangel, M. G., Khurana, A., Goff, D. C., Stickgold, R. (2004): A failure of sleep-dependent procedural learning in chronic, medicated schizophrenia. *Biological Psychiatry*, *56*, 951–956.
- Marcus, D. S., Van Essen, D. C. (2002): Scene segmentation and attention in primate cortical areas V1 and V2. *Journal of Neurophysiology*, *88*, 2648–2658.
- McMains, S. A., Kastner, S. (2010): Defining the units of competition: Influences of perceptual organization on competitive interactions in human visual cortex. *Journal of Cognitive Neuroscience*, *22*, 2417–2426.
- McMains, S., Kastner, S. (2011): Interactions of top-down and bottom-up mechanisms in human visual cortex. *Journal of Neuroscience*, *31*, 587–597.
- Mednick, S. C., Nakayama, K., Cantero, J. L., Atienza, M., Levin, A. A., Pathak, N., Stickgold, R. (2002): The restorative effect of naps on perceptual deterioration. *Nature Neuroscience*, *5*, 677–681.
- Minzenberg, M. J., Poole, J. H., Benton, C., Vinogradov, S. (2004): Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *American Journal of Psychiatry*, *161*, 116–124.
- Must, A., Janka, Z., Benedek, G., Kéri, S. (2004): Reduced facilitation effect of collinear flankers on contrast detection reveals impaired lateral connectivity in the visual cortex of schizophrenia patients. *Neuroscience Letters*, *357*, 131–134.
- Nuechterlein, K. H. (1977): Reaction time and attention in schizophrenia: A critical evaluation of the data and theories. *Schizophrenia Bulletin*, *3*, 373–428.
- Olney, J. W., Newcomer, J. W., Farber, N. B. (1999): NMDA receptor hypofunction model of schizophrenia. *Journal of Psychiatric Research*, *33*, 523–533.
- Palmer, S. E. (1999): *Vision Science: From Photons to Phenomenology*. Cambridge, MA: MIT Press.
- Palmer, S. E., Brooks, J. L., Nelson, R. (2003): When does grouping happen? *Acta Psychologica* (Amsterdam), *114*, 311–330.
- Paul, G. L., Lentz, R. J. (1977): *Psychosocial Treatment of Chronic Mental Patients: Milieu versus Social Learning Programs*. Cambridge, MA: Harvard University Press.
- Peled, A. (2004): From plasticity to complexity: A new diagnostic method for psychiatry. *Medical Hypotheses*, *63*, 110–114.
- Pennefather, P. M., Chandna, A., Kovács, I., Polat, U., Norcia, A. M. (1999): Contour detection threshold: Repeatability and learning with ‘contour cards’. *Spatial Vision*, *12*, 257–266.
- Phillips, W. A., Silverstein, S. M. (2003): Impaired cognitive coordination in schizophrenia: Convergence of neurobiological and psychological perspectives. *Behavioral and Brain Sciences*, *26*, 65–137.
- Phillips, W. A., Singer, W. (1997): In search of common foundations for cortical computation. *Behavioral and Brain Sciences*, *20*, 657–722.
- Piccini, C., Lauro-Grotto, R., Del Viva, M., Burr, D. (2003): Agnosia for global patterns: When the cross-talk between grouping and visual selective attention fails. *Cognitive Neuropsychology*, *20*, 3–25.
- Pinto, J. G. A., Hornby, K. R., Jones, D. G., Murphy, K. M. (2010): Developmental changes in GABAergic mechanisms in human visual cortex across the lifespan. *Frontiers in Human Neuroscience*, *4*, 16.
- Place, E. J., Gilmore, G. C. (1980): Perceptual organization in schizophrenia. *Journal of Abnormal Psychology*, *89*, 409–418.
- Poggio, T., Fahle, M., Edelman, S. (1992): Fast perceptual learning in visual hyperacuity. *Science*, *256*, 1018–1021.

- Pomerantz, J. R., Kubovy, M. (1986): Theoretical approaches to perceptual organization: Simplicity and likelihood principles. In Boff, K. R., Kauffman, L., Thomas, J. P. (eds), *Handbook of Perception and Human Performance, Volume 2, Cognitive Processes and Performance*. New York: Wiley, pp. 36:1 to 36:46.
- Proksch, J., Bavelier, D. (2002): Changes in the spatial distribution of visual attention after early deafness. *Journal of Cognitive Neuroscience*, *14*, 687–701.
- Quinn, P. C., Bhatt, R. S. (2009): Perceptual organization in infancy: Bottom-up and top-down influences. *Optometry and Vision Science*, *86*, 589–594.
- Rainer, G., Miller, E. K. (2000): Effects of visual experience on the representation of objects in the prefrontal cortex. *Neuron*, *27*, 179–189.
- Razpurker-Apfeld, I., Pratt, H. (2008): Perceptual visual grouping under inattention: Electrophysiological functional imaging. *Brain and Cognition*, *67*, 183–196.
- Roelfsema, P. R. (2006): Cortical algorithms for perceptual grouping. *Annual Review of Neuroscience*, *29*, 203–227.
- Roopun, A. K., Cunningham, M. O., Racca, C., Alter, K., Traub, R. D., Whittington, M. A. (2008): Region-specific changes in gamma and beta2 rhythms in NMDA receptor dysfunction models of schizophrenia. *Schizophrenia Bulletin*, *34*, 962–973.
- Rubin, N., Nakayama, K., Shapley, R. (2002): The role of insight in perceptual learning: Evidence from illusory contour perception. In Fahle, M., Poggio, T. (eds), *Perceptual Learning*. Cambridge, MA: MIT Press, pp. 235–251.
- Sabatino, M., Cromwell, H. C., Cepeda, C., Levine, M. S., La Grutta, V. (1999): Acetylcholine receptor activation enhances NMDA-mediated responses in the rat neostriatum. *Neurophysiologie Clinique*, *29*, 482–489.
- Sagi, D., Kovács, I., Racsmány, M. (2009): Preface. *Learning and Perception*, *1*, 1–2.
- Schenkel, L. S., Spaulding, W. D., Silverstein, S. M. (2005b): Poor premorbid social functioning and theory of mind deficit in schizophrenia: Evidence of reduced context processing? *Journal of Psychiatric Research*, *39*, 499–508.
- Schenkel, L. S., DiLillo, D., Spaulding, W. D., Silverstein, S. M. (2005a): Histories of childhood maltreatment in schizophrenia: Relationships with premorbid functioning, symptomatology, and cognitive deficits. *Schizophrenia Research*, *76*, 273–286.
- Schiltz, C., Bodart, J. M., Dubois, S., Dejardin, S., Michel, C., Roucoux, A., Crommelinck, M., Orban, G. A. (1998): Neuronal mechanisms of perceptual learning: Changes in human brain activity with training in orientation discrimination. *NeuroImage*, *9*, 46–62.
- Sehatpour, P., Molholm, S., Javitt, D. C., Foxe, J. J. (2006): Spatiotemporal dynamics of human object recognition processing: An integrated high-density electrical mapping and functional imaging study of “closure” processes. *Neuroimage*, *29*, 605–618.
- Sheinberg, D. L., Logothetis, N. K. (2002): Perceptual learning and the development of complex visual representations in temporal cortical neurons. In Fahle, M., Poggio, T. (eds), *Perceptual Learning*. Cambridge, MA: MIT Press, pp. 95–124.
- Shulman, G. L. (1992): Attentional modulation of size contrast. *Quarterly Journal of Experimental Psychology A*, *45*(4), 529–546.
- Silverstein, S. M. (2010): Failures of dynamic coordination in disease states, and their implications for normal brain function. In Singer, W., Malsburg, C. V. D., Phillips, W. A. (eds), *Dynamic Coordination in the Brain: From Molecules to Mind: Ernst Strüngmann Forum Report #5*. Cambridge, MA: MIT Press, pp. 245–265.
- Silverstein, S. M., Schenkel, L. (1997): Schizophrenia as a model of context-deficient cortical computation. *Behavioral and Brain Sciences*, *20*, 696–697.

- Silverstein, S. M., Matteson, S., Knight, R. A. (1996): Reduced top-down influence in auditory perceptual organization in schizophrenia. *Journal of Abnormal Psychology*, *105*, 663–667.
- Silverstein, S. M., Spaulding, W. D., Menditto, A. A. (2006): *Schizophrenia: Advances in Evidence-based Practice*. Cambridge, MA: Hogrefe Huber.
- Silverstein, S. M., Bakshi, S., Chapman, R. M., Nowlis, G. (1998): Perceptual organization of configural and nonconfigural visual patterns in schizophrenia: Effects of repeated exposure. *Cognitive Neuropsychiatry*, *3*, 209–223.
- Silverstein, S. M., Kovács, I., Corry, R., Valone, C. (2000): Perceptual organization, the disorganization syndrome, and context processing in chronic schizophrenia. *Schizophrenia Research*, *43*, 11–20.
- Silverstein, S. M., Schenkel, L. S., Valone, C., Nuernberger, S. W. (1998): Cognitive deficits and psychiatric rehabilitation outcomes in schizophrenia. *Psychiatric Quarterly*, *69*, 169–191.
- Silverstein, S. M., Bakshi, S., Nuernberger, S., Carpiniello, K., Wilkniss, S. (2005): Effects of stimulus structure and target-distracter similarity on the development of visual memory representations in schizophrenia. *Cognitive Neuropsychiatry*, *10*, 215–229.
- Silverstein, S. M., Berten, S., Essex, B., All, S. D., Kasi, R., Little, D. M. (2010b): Perceptual organization and visual search processes during target detection task performance in schizophrenia, as revealed by fMRI. *Neuropsychologia*, *48*, 2886–2893.
- Silverstein, S. M., Berten, S., Essex, B., Kovács, I., Susmaras, T., Little, D. M. (2009): An fMRI examination of visual integration in schizophrenia. *Journal of Integrative Neuroscience*, *8*, 175–202.
- Silverstein, S. M., Wong, M-H., Wilkniss, S. M., Bloch, A., Smith, T. E., Savitz, A., McCarthy, R., Terkelsen, K. (2006a): Behavioral rehabilitation of the “treatment-refractory” schizophrenia patient: Conceptual foundations, interventions, interpersonal techniques, and outcome data. *Psychological Services*, *3*, 145–169.
- Silverstein, S. M., Hatashita-Wong, M. H., Schenkel, L. S., Kovács, I., Feher, A., Smith, T. E., Goicochea, C., Uhlhaas, P. (2006b): Reduced top-down influences in contour detection in schizophrenia. *Cognitive Neuropsychiatry*, *11*, 112–132.
- Silverstein, S. M., Keane, B. P., Barch, D. M., Carter, C. C., Gold, J., Kovács, I., MacDonald, A. W. III, Ragland, J. D., Strauss, M. E.: Optimization and validation of a visual integration test for use in schizophrenia research. *Schizophrenia Bulletin*. (In press)
- Silverstein, S. M., Barch, D., Carter, C., Dakin, S., Gold, J., Kovács, I., Luck, S., MacDonald, A., Ragland, J. D., Ranganath, C., Strauss, M. (2010a): Translational development and psychometric comparison of two visual integration tasks. *Biological Psychiatry*, *67* (Supplement 9S), 111S.
- Singer, W. (1995): Development and plasticity of cortical processing architectures. *Science*, *270*, 758–764.
- Sinha, P., Poggio T. (1996): Role of learning in three-dimensional form perception. *Nature*, *384*, 460–463.
- Sinha, P., Poggio, T. (2002): High-level learning of early visual tasks. In Fahle, M., Poggio, T. (eds), *Perceptual Learning*. Cambridge, MA: MIT Press, pp. 273–298.
- Sireteanu, R., Rettenbach, R. (2000): Perceptual learning in visual search generalizes over tasks, locations, and eyes. *Vision Research*, *40*, 2925–2949.
- Snyder, S. (1961): Perceptual closure in acute paranoid schizophrenics. *Archives of General Psychiatry*, *5*, 406–410.
- Snyder, S., Rosenthal, D., Taylor, A. (1961): Perceptual closure in schizophrenics. *Journal of Abnormal and Social Psychology*, *63*, 131–136.
- Sowden, P. T., Davies, I. R. L., Roling, P. (2000): Perceptual learning of the detection of features in X-ray images: A functional role for improvements in adults’ visual sensitivity? *Journal of Experimental Psychology: Human Perception and Performance*, *26*, 379–390.

- Spencer, K. M. (2009): The functional consequences of cortical circuit abnormalities on gamma oscillations in schizophrenia: Insights from computational modeling. *Frontiers in Human Neuroscience*, 3, 33.
- Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., McCarley, R. W. (2003): Abnormal neural synchrony in schizophrenia. *The Journal of Neuroscience*, 23, 7407–7411.
- Spencer, K. M., Nestor, P. G., Perlmuter, R., Niznikiewicz, M. A., Klump, M. C., Frumin, M., Shenton, M. E., McCarley, R. W. (2004): Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proceedings of the National Academy of Sciences U S A*, 101, 17288–17293.
- Stickgold, R., James, L. T., Hobson, J. A. (2000): Visual discrimination learning requires sleep after training. *Nature Neuroscience*, 3, 1237–1238.
- Teich, A. F., Qian, N. (2010): V1 orientation plasticity is explained by broadly tuned feedforward inputs and intracortical sharpening. *Visual Neuroscience*, 27, 57–73.
- Trujillo, L. T., Allen, J. J., Schnyer, D. M., Peterson, M. A. (2010): Neurophysiological evidence for the influence of past experience on figure-ground perception. *Journal of Vision*, 10, 5.1–21.
- Uhlhaas, P. J., Silverstein, S. M. (2005): Perceptual organization in schizophrenia spectrum disorders: A review of empirical research and associated theories. *Psychological Bulletin*, 131, 618–632.
- Uhlhaas, P. J., Singer, W. (2006): Neural synchrony in brain disorders: Relevance for cognitive dysfunctions and pathophysiology. *Neuron*, 52, 155–168.
- Uhlhaas, P. J., Phillips, W. A., Silverstein, S. M. (2005): The course and clinical correlates of dysfunctions in visual perceptual organization in schizophrenia during the remission of psychotic symptoms. *Schizophrenia Research*, 72, 183–192.
- Uhlhaas, P. J., Haenschel, C., Nikolić, D., Singer, W. (2008): The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. *Schizophrenia Bulletin*, 34, 927–943.
- Uhlhaas, P. J., Phillips, W. A., Mitchell, G., Silverstein, S. M. (2006b): Perceptual grouping in disorganized schizophrenia. *Schizophrenia Research*, 145, 105–117.
- Uhlhaas, P. J., Silverstein, S. M., Phillips, W. A., Lovell, P. G. (2004): Evidence for impaired visual context processing in schizotypy with thought disorder. *Schizophrenia Research*, 68, 249–260.
- Uhlhaas, P. J., Roux, F., Rodriguez, E., Rotarska-Jagiela, A., Singer, W. (2010): Neural synchrony and the development of cortical networks. *Trends in Cognitive Neurosciences*, 14, 72–80.
- Uhlhaas, P. J., Linden, D. E., Singer, W., Haenschel, C., Lindner, M., Maurer, K., Rodriguez, E. (2006a): Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *Journal of Neuroscience*, 26, 8168–8175.
- Uhlhaas, P. J., Pipa, G., Lima, B., Melloni, L., Neuenschwander, S., Nikolić, D., Singer, W. (2009): Neural synchrony in cortical networks: History, concept and current status. *Frontiers in Integrative Neuroscience*, 3, 17.
- Viggiano, M. P., Kutas, M. (2000): Overt and covert identification of fragmented objects inferred from performance and electrophysiological measures. *Journal of Experimental Psychology: General*, 129, 107–125.
- Wagemans, J. (1995): Detection of visual symmetries. *Spatial Vision*, 9, 9–32.
- Windmann, S., Wehrmann, M., Calabrese, P., Gunturkun O. (2006): Role of the prefrontal cortex in attention control over bistable vision. *Journal of Cognitive Neuroscience*, 18, 456–471.
- Yashiro, K., Philpot, B. D. (2008): Regulation of NMDA receptor subunit expression and its implications for LTD, LTP, and metaplasticity. *Neuropharmacology*, 55, 1081–1094.
- Yoon, J. H., Maddock, R. J., Rokem, A., Silver, M. A., Minzenberg, M. J., Ragland, J. D., Carter, C. S. (2010): GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *Journal of Neuroscience*, 30, 3777–3781.

- Yotsumoto, Y., Watanabe, T., Sasaki, Y. (2008): Different dynamics of performance and brain activation in the time course of perceptual learning. *Neuron*, 57, 827–833.
- Zemel, R. S., Behrmann, M., Mozer, M. C., Bavelier, D. (2002): Experience-dependent perceptual grouping and object-based attention. *Journal of Experimental Psychology: Human Perception and Performance*, 28(1), 200–217.
- Zenger, B., Sagi, D. (2002): Plasticity of low-level visual networks. In Fahle, M., Poggio, T. (eds), *Perceptual Learning*. Cambridge, MA: MIT Press, pp. 177–196.
- Zhou, J., Tjan, B. S., Zhou, Y., Liu, Z. (2008): Better discrimination for illusory than for occluded perceptual completions. *Journal of Vision*, 8(7):26, 1–17, <http://journalofvision.org/8/7/26/>, doi:10.1167/8.7.26.