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Perceptual Organization Impairment in Schizophrenia and Associated Brain Mechanisms: Review of Research from 2005 to 2010

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Perceptual organization (PO) refers to the processes by which visual information is structured into coherent patterns such as groups, contours, perceptual wholes, and object representations. Impairments in PO have been demonstrated in schizophrenia since the 1960s and have been linked to several illness-related factors including poor premorbid functioning, poor prognosis, and disorganized symptoms. This literature was last reviewed in 2005. Since then, electrophysiological (electroencephalographic, event-related potential, and magnetoencephalographic) and fMRI studies in both patient and nonpatient samples have clarified brain mechanisms involved in the impairment, and additional behavioral studies in patients and nonpatients have clarified the computational mechanisms. In addition, data now exist on the functional consequences of PO impairments, in terms of secondary difficulties in face processing, selective attention, working memory, and social cognition. Preliminary data on drug effects on PO and on changes in response to treatment suggest that anomalies in PO may furnish a biomarker for the integrity of its associated biological mechanisms. All of this recent evidence allows for a clearer picture of the nature of the impairment and how it relates to broader aspects of brain and behavioral functioning in schizophrenia.

Key words: schizophrenia/perception/disorganization/cognition/cognitive/neuroscience/binding/integration

Perceptual organization (PO) refers to the processes by which visual information is structured into coherent patterns such as groups, contours, perceptual wholes, and object representations. Demonstrations of PO impairment in schizophrenia go back to the early 1960s, with a rapid increase since the early 1980s. This literature was last reviewed in 2005.[1] However, findings since that time have continued to clarify the nature of the impairment and have significantly advanced our understanding of its underlying brain mechanisms and functional consequences. The purpose of this article is to review these recent findings. First, however, the clinical relevance of PO impairment will be established, and major research findings from before 2005 will be briefly summarized.

The Clinical Relevance of Perceptual Organization Dysfunction in Schizophrenia

Beginning in the 1950s, a number of writers suggested that visual perception disturbances are among the most significant features of the disorder. One of the disturbances described by several authors involved fragmented visual perception, as described in the following example: ''I have to put things together in my head. If I look at my watch I see the watch, watchstrap, face, hands, and so on, then I have got to put them together to get it into one piece.[2] (p229)'' In addition to seeing objects as fragmented, scenes could be perceived as fragmented. This can be seen in the following example: ''I only saw fragments: a few people, a kiosk, a house. To be quite correct, I cannot say that I see all of that, because the objects seemed altered from the usual. They did not stand together in an overall context, and I saw them as meaningless details.[3] (p92)'' These examples indicate that, in schizophrenia, there are varying degrees of impairment in PO, from disturbances in the coherence within a scene to a splitting of object parts.

Summary of pre-2005 Data

Uhlhaas and Silverstein[1] reviewed the literature on PO in schizophrenia from 1975 to 2004. That review noted that 28 of 33 studies indicated deficient PO in schizophrenia. In general, the impairment was most pronounced when

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processing novel, fragmented stimuli within noise, and therefore where top-down input is required to produce grouping in the absence of strong stimulus-driven cues. The 5 studies that did not find evidence of PO impairment typically used stimuli that were highly symmetrical and/or nonfragmented (eg, closed triangles), and therefore that could be processed via prespecified feature hierarchies[4] (ie, activity from V1 simple cell classical receptive fields is combined in a manner prespecified by existing connections between these cells to compute, in an obligatory manner, output representing the combination of the features signaled—as is the case for parallelism, symmetry, and visual primitives such as angles formed by 2 line segments) that develop very early in life.[5] Taken together, the data indicated an impairment in dynamic grouping in schizophrenia, which can be defined as the flexible and adaptive process by which the visual system creates novel higher order representations in which global stimulus structure is represented.[4] Importantly, PO impairments in schizophrenia are not secondary to problems in feature processing, V1 activation, or contrast sensitivity because either group differences in these processes have been shown not to exist (see below, fMRI studies) or these sources of variance in PO test scores have been ruled out in studies of nonschizophrenia populations (see online supplementary references).

Multiple studies have demonstrated that PO dysfunction in schizophrenia is most pronounced in a subtype of patient characterized by poor premorbid social functioning, increased levels of disorganization, and/or poor outcome—factors that are themselves associated and that have been linked to familial schizophrenia (see online supplementary references). In one study, PO dysfunction was linked to elevated nailfold plexus visibility (a biological marker of schizophrenia that has also been linked to poor outcomes).

An important finding from the 2005 review[1] was that in 10 studies schizophrenia patients performed better than control subjects—a scenario created by designing the task so that normal PO would interfere with the ability to identify or make judgments about single stimuli that were grouped with irrelevant features. Therefore, findings of PO impairment in schizophrenia have been convincingly demonstrated independently of a generalized deficit. In addition, the findings could not be attributed to medication effects because they had been observed in unmedicated patients, and dose and task performance did not covary when this was measured.

Behavioral Findings, 2005–2010

Below, we will describe findings from studies that investigated PO using computerized stimulus presentation and tasks grounded in cognitive neuroscience. We will not discuss findings from global-local tasks because these primarily investigate switching of attention between levels, except in cases where the results have a direct bearing on PO in schizophrenia.

Task Performance

Recent studies have demonstrated impairments in contour integration,[6–13] perception of fragmented drawings,[14] pattern recognition,[15] grouping of dot patterns by proximity and color similarity,[16] configural processing of faces (in both patients[17–19] and people at high-risk for schizophrenia[20]), and coherent integration of moving stimuli.[21–24] In addition, schizophrenia patients were less impaired when targets and distractors were grouped by being inside a closed figure.[25] Patients were also less augmented by collinear grouping in a detection task.[26–28] One study reported normal PO,[29] however, this conclusion was based on normal effects of changing the ratio of different types of distractors (which could be more or less similar to targets, thereby presumably affecting PO via grouping-by-similarity effects) on visual search, and so this is a less direct test of PO than the studies reported above. This study's results also differ from others that demonstrated impaired top-down influence during visual search. It is also possible that such findings could be related to the increased decision-making requirements involved with increasing distractors,[30] and recent data indicate impairments in decision making and response preparation processes during PO tasks in schizophrenia patients.[31]

Similar to that noted in earlier reviews, data from multiple recent studies suggest that a major factor in PO impairments in schizophrenia is reduced or impaired top-down feedback to perceptual processes. The role of top-down influences (eg, expectation, memory, attention) in PO is now well established. PO is sensitive to top-down influences as long as there is sufficient time for feedback to operate,[32] which was the case in all studies reported here, as stimulus presentation was supraliminal and unmasked in all cases. Reduced top-down feedback was demonstrated in the form of reduced sensitivity to repetition,[15] stimulus presentation,[33] and condition ordering.[12] In addition, because vulnerability to the Ebbinghaus illusion (see figure 1) is known to be affected by extent of visual experience judging perspective from 2D images, reduced sensitivity of schizophrenia patients to this illusion[10] (leading to more accurate performance judging the size of a circle that is surrounded by either larger or smaller circles) can be taken as evidence of a reduced impact of prior knowledge on PO (see also Horton and Silverstein[34]). Interestingly, however, reduced top-down effects appear to be greatest during single-session performance. Learning effects on PO in schizophrenia over multiple days appear to be equivalent in patients and controls, at least for stimuli where patients can achieve PO in an initial session.[12]

There is also some (but not as much) evidence that PO impairments in schizophrenia arise from impaired

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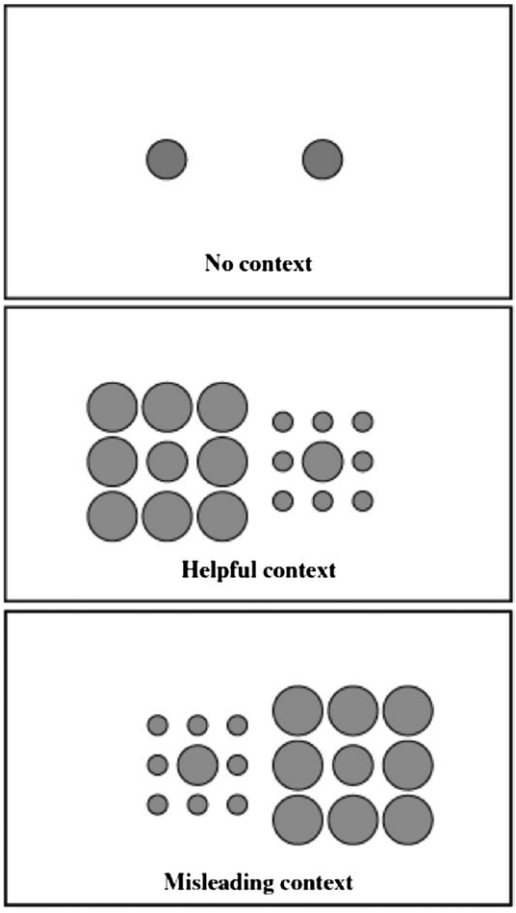

Fig. 1. Examples of stimuli from an Ebbinghaus illusion task. On each trial, subjects have to judge which center circle is larger (on control trials, no surrounding circles are present). Note in this figure, in each row, the center circle on the right is 2% larger than the center circle on the left.

bottom-up processing. In a collinear facilitation paradigm, healthy subjects better detect a central low-contrast Gabor target when it is flanked by 2 collinear (rather than orthogonal) high-contrast Gabors. Schizophrenia (but not bipolar disorder) patients failed to exhibit collinear facilitation and this did not depend on medication status.[26,28] The deficit cannot be blamed on insufficient attention, because the patients performed the same as controls on a secondary task that required making use of the collinear flankers.[26] In addition, in Kourtzi et al's[35] fMRI studies of contour integration, similar visual cortex effects (see below, section on fMRI) were observed in awake humans and anesthetized monkeys, with the latter suggesting that attentional and cognitive control processes are not necessary for multi-element integration to occur, at least for this basic type of PO. Future studies will need to more conclusively determine the contribution of bottom-up grouping failures to the PO impairment in schizophrenia, and this can be done, eg, by using object tracking, visual search, and shape discrimination tasks.

Links with Symptoms

It was noted in multiple earlier articles and reviews that PO impairments in schizophrenia were linked with disorganized, but not positive or negative, symptoms. The few studies from 2005 to 2010 that reported on cognition-symptom relationships also demonstrated this relationship.[6,7,10,11,36] One article reported a relationship between PO impairment and negative symptoms.[27] Interestingly, this article examined linking of an element with 2 flankers, whereas studies that reported relationships with disorganized symptoms employed tasks in which a fragmented (entire) shape or object image had to be organized.

Course of Illness

Using a task that was sensitive to PO impairments in patients in multiple past studies, PO was found to be normal in first episode patients and people at ultrahigh risk for the disorder.[37] This is consistent with a small amount of past research (reviewed in ref. Uhlhaas and Silverstein[1]) that found normal PO in psychometrically defined high-risk groups, prodromal patients, and at first episode. These data suggest that PO impairment reflects illness progression, especially in light of consistent findings of PO impairment in later-episode patients, and predictive relationships between PO and discharge status from a state hospital after 3 years (Uhlhaas and Silverstein[1]).

Treatment Effects

To date, there have been no pharmacological challenge or cognitive rehabilitation studies that examined PO as an outcome variable. However, evidence that level of PO is sensitive to medication effects comes from 2 studies. In one,[11] patients were tested on admission to an acute care inpatient unit and then again at discharge (~3 weeks later). For disorganized schizophrenia patients, the only group that demonstrated impairment on admission, performance improved significantly during treatment. Moreover, degree of normalization of PO was significantly correlated with degree of reduction of disorganized (but not positive or negative) symptoms. In a second study, ketamine (a noncompetitive *N*-methyl-D-aspartate [NMDA] receptor antagonist) users were tested on a contour integration test the night of ketamine use and then again 3 days later.[38] Task performance was abnormal only on the night of ketamine use. These data are consistent with the hypothesis that PO impairment is related to altered cognitive coordination (ie, context-based modulation of feedforward input),[39] secondary to NMDA receptor hypofunction and possibly associated reduced input onto inhibitory *gamma*-aminobutyric acid (GABA)-mediated interneurons (see below, section on cognitive coordination, and online supplementary information for relevant references).

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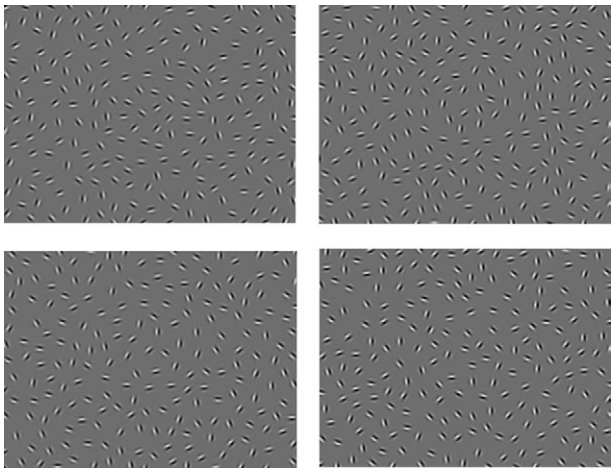

Fig. 2. Samples of images from the contour integration task. Top left: 0° jitter, top right: 7°–8° jitter, bottom left: 11°–12° jitter, bottom right: 15°–16° jitter.

fMRI Studies

Silverstein et al[13] demonstrated that outpatients with schizophrenia performed more poorly on a contour integration task than healthy controls and that this was associated with abnormalities in brain activation. In this study, subjects discriminated the pointing direction (left vs right) of an egg-shaped target, the edges of which were defined by spatially separated Gabors. Task difficulty was manipulated by jittering the orientation of the contour elements either +/− 0°, 7°, 11°, 15°, 19°, or 23° from their original position (see figure 2). Analysis of changes in BOLD signal relative to baseline indicated that, for both groups, early visual areas (V1–V4) were sensitive to the jitter manipulation, with BOLD signal increasing systematically across the first few conditions where contour perception became more difficult but was still possible. In higher visual areas, however (eg, inferotemporal cortex), activation did not vary as a function of jitter level. Within this context, patients demonstrated significantly less activation than controls at all jitter conditions in V2/V3 and V4, but not in V1 (see figure 3). Moreover, the size of the between-group difference in activation (collapsed across jitter conditions) increased from V1 to V4. These data were consistent with earlier data on contour integration in healthy humans and in monkeys that identified early visual regions (eg, V1–V4), as the loci for contour integration effects (eg,Kourtzi et al[35]). They also fit with data suggesting that V1 is involved in processing smaller-scale groupings of collinear and nearby elements, whereas processing of larger regions of contour, including curvature effects—requiring greater demands on integration and so where schizophrenia patients would be expected to demonstrate relatively more difficulty—occurs increasingly from V2 through V4.[40] These same regions also appear to be the basis for PO based on temporal synchrony.[41] In addition, the data fit with prior findings of (1) reduced connectivity and diminished synaptic signaling in the visual cortex in schizophrenia; (2) white matter reductions in visual cortex in schizophrenia, especially in early regions; (3) gray matter abnormalities in occipital cortex in children and adults with amblyopia, an ophthalmologic condition associated with abnormal development of early visual cortex regions, that is one of the only other conditions where PO deficits have been demonstrated (see Silverstein[42] for review); and (4) gray matter loss in the occipital lobe in patients with schizophrenia, especially for "poor outcome" patients,[43] who are typically those demonstrating the most significant PO impairments.

In the Silverstein et al[13] study, contrasts between conditions where contours could be perceived and conditions where they could not indicated that, in addition to activation differences in the visual cortex regions noted above, controls were more active, compared with patients, in prefrontal and parietal regions involved in object-based attention, as well as in the superior, middle, and inferior temporal gyri, areas involved in visual form perception. It should be noted that these effects were not due to a generalized hypoactivity in schizophrenia because patients demonstrated more activity than controls in some of these areas when the opposite contrast was performed. These differences were observed

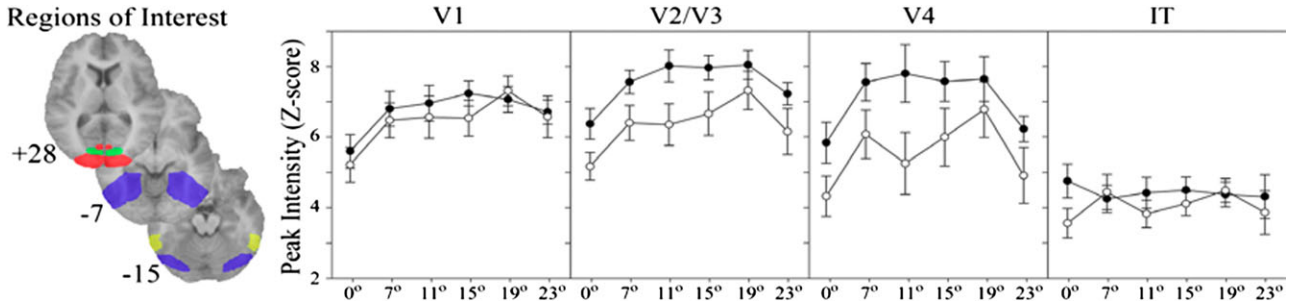

Fig. 3. Regions of interest for extraction of the peak signal change (Y-axis) within V1 (green), V2/V3 (red), V4 (blue), and inferotemporal cortex (IT) (yellow). Peak signal intensity for controls (black circles) and patients (white circles) for areas involved in visual processing. X-axis depicts degree of orientation jitter of contour elements. Figure reprinted with permission from Imperial College Press.[13]

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even when the groups were matched on level of behavioral performance. These data suggested that PO impairment in schizophrenia is not solely a function of underactivation of occipital regions involved in visual integration, but rather, that it involves reduced functioning in a network of regions involving form perception, attentional capture by novel stimuli, and attentional enhancement of coherent forms relative to background information. A similar conclusion was reached by Sehatpour et al[14] (see also below, section on event-related potential [ERP] findings) from an integrated ERP and fMRI study of PO. Here, fMRI data indicated abnormal activity in a network involving the dorsal and ventral visual regions, prefrontal cortex (PFC), and hippocampus. More specifically, the data suggested that impaired activation of dorsal stream visual regions contributed to reduced PFC activation, which, in turn, contributed to reduced activation of the hippocampus and ventral visual stream. These data suggesting postoccipital contributions to PO impairment in schizophrenia are supported by recent evidence on the role of areas of outside the occipital cortex in PO. For example, neuropsychological data suggest that (1) activation within the temporo-parietal junction is necessary for target-noise segregation when global perception cannot be achieved via local cortico-cortical interactions; (2) areas within the parietal cortex are involved in PO in audition and vision (as revealed by positron emission tomography and repetitive transcranial magnetic stimulation); (3) the prefrontal cortex is necessary to main a representation of visual stimuli in extrastriate visual areas; and (4) patients with PFC lesions demonstrate PO deficits (see Silverstein[42] for review). It should be noted, however, that not all studies support the role of the dorsal visual stream in PO. For example, a recent fMRI study in healthy subjects did not find effects of PO in the dorsal stream even though expected ventral stream activity was observed.[44] The most likely explanation for differences in brain activation during PO across studies is that different forms of PO (eg, early vs later; based on feature similarity vs based on top-down factors) recruit different combinations of brain regions—as indicated by EEG studies (see next section).

A potential consequence of reduced activity in V2–V4 is compensatory activation in higher visual areas. For example, in the Silverstein et al[13] contour integration study noted above, controls were more active in V2/V3, whereas patients demonstrated more activation in the fusiform gyrus and V5. In another study,[17] patients performed more poorly than controls when processing global components of face stimuli (ie, low spatial frequency information). Here, controls demonstrated greater activation than patients in early visual cortex regions, whereas patients demonstrated greater activation than controls in the middle temporal gyrus and left fusiform gyrus. We interpret data from these 2 studies as evidence that, among patients, deficient processing in early visual regions was compensated for, in part, by greater activity in higher visual areas. These data cannot be accounted for by a general hypo-activity of the visual cortex in schizophrenia since, in both studies, in conditions where global information was relatively absent, patients demonstrated increased early visual cortex activity compared with controls.

In summary, recent fMRI studies of PO in schizophrenia indicate that impaired behavioral performance is associated with reduced activity in extrastriate visual cortex regions, in addition to more anterior areas involved in form processing and object-based attention (eg, temporal gyri, parietal, and frontal regions). These findings are supported by data from electrophysiological studies, to which we now turn.

Recent EEG/ERP/MEG Findings

Electrophysiological data from healthy subjects indicate that PO is a multi-stage process that cannot be localized to a specific brain region or time period. Electrical correlates of PO occur both early (ie, in the first 100 ms after stimulus onset, as reflected by, eg,, P1 or P100) as well as late (ie, 300–400 ms after stimulus onset or even later), and over different brain regions. This is consistent with theory and behavioral data that PO occurs at multiple processing stages and on multiple forms of representations depending on the nature of the stimuli and task (ie, the extent to which grouping can occur via prespecified feature hierarchies) and requirements for top-down feedback (eg, from memory, strategy, etc.) to visual processes. In some cases, ERP indices of PO are thought to reflect feature binding, whereas in others, they are thought to reflect lateral and feedback interactions associated with conscious awareness of and attention to the stimulus. Consistent with this evidence, recent electrophysiological data indicate multiple temporal windows and brain regions associated with reduced PO in schizophrenia. For example, Foxe et al,[45] in a study of illusory contour processing in which patients performed normally on the behavioral task, found reduced amplitude and topographic differences in P1 among patients compared with healthy controls, which were associated with reduced flow of information into dorsal visual processing areas. Patients also demonstrated increased frontal activity, which was interpreted as compensation for impaired ventral stream processing during the later stages of PO. Johnson et al[46] observed reduced N150 amplitude during impaired global form processing—a waveform that has been identified as originating in and near areas V3/V3a in extrastriate visual cortex. The adjacent lateral occipital complex (LOC) was found to be the generator of a later negativity called "closure negativity" (NCl) that is involved in PO, with fMRI and ERP indices of NCl identifying identical generator regions of the LOC.[47] Sehatpour, in the integrated fMRI and ERP study of PO noted in the section above, found impairments in both

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early sensory processing (eg, P1) and later (NCl) closure-related activity in schizophrenia.[14]

In addition to studies of specific waveforms, the past decade has seen an increase in studies of power and synchrony of oscillations within specific frequency bands. Earlier data in healthy humans and animals suggested that synchrony within the gamma (30–100 Hz) band was a neural correlate of PO. Studies prior to 2005 observed reduced gamma-band synchrony during illusory contour processing in schizophrenia. More recently, in an EEG study, Uhlhaas and colleagues[48] found reduced beta-band (20–30 Hz) synchrony during a PO (Mooney Faces) task among schizophrenia patients. In particular, patients demonstrated reduced synchrony between fronto-temporal and between parieto-occipital electrodes compared with controls. Other studies from this group, using EEG or MEG, indicate the role of - occipital, temporal, and parietal regions, and synchronization within the gamma band, in processing the stimuli used in the study noted above with schizophrenia patients, as well as important sequential interactions between the inferior temporal cortex, posterior parietal cortex, and fusiform gyrus. Taken together, electrophysiological data support fMRI data in indicating that PO impairment in schizophrenia reflects problems with both early and later stages of visual processing; these stages require occipital activity, as part of broader networks with temporal, parietal, and frontal regions involved in form perception and object-based attention. The extent of involvement of these nonoccipital regions is determined by the nature and complexity of the stimuli, as well as the requirements for attention and input from memory and strategic planning processes.

Additional Issues

Consequences of PO Impairments in Schizophrenia

Relatively little work has explored the effects of PO impairment on cognitive and behavioral functioning. However, evidence for such influences exists. For example, Giersch and Rhein,[33] in a study showing reduced top-down control of PO in schizophrenia, demonstrated that this led to poorer selective attention for relevant visual stimuli compared with controls. Specifically, reduced PO led to reduced allocation of attention within grouping-defined target objects, and a more diffuse "spread" of attention across objects. The role of PO in working memory has also been described in healthy subjects, and a recent study of working memory in schizophrenia found that reduced grouping of moving and static visual displays was related to poorer visuo-spatial working memory.[24] This supported an earlier study in which patients failed to develop visual memory representations for poorly organized stimuli.[15] Both of these studies demonstrate that reduced PO is a rate-limiting factor for effective encoding in working memory. PO has also been found to contribute to face processing, a process known to be impaired in schizophrenia. For example, processing of the configural aspects of faces has been found to be impaired in both patients[17–19] and in young people at ultrahigh risk for the disorder.[20] Moreover, a - recent ERP study demonstrated reduced facial emotion recognition performance in schizophrenia patients, and this was associated with reduced N170, a waveform associated with structural encoding of visual features, but not N250, which has been associated with affect recognition.[49] This combination of findings led Turetsky et al[49] to conclude that emotion recognition difficulties in schizophrenia are downstream consequences of a problem in integrating facial feature information. A potential consequence of a reduced ability to process emotional information from faces is impairment in inferring the mental states of others or a reduced ability to generate a theory of mind. Indeed, PO impairment has predicted deficient theory of mind ability in schizophrenia in 2 studies.[6,8] Also, as noted in the Introduction, Mattusek, in clinical vignettes, reported that in schizophrenia, objects are sometimes not perceived as being grouped with their proper context, but rather, they can stand out and assume unusual significance for the patient. Conversely, objects and the environment as a whole may appear to have lost their meaning due to the grouping impairment. Evidence for this was recently provided by Talamini et al[50], who demonstrated that schizophrenia patients are less affected by scene contexts during encoding of object information, leading to fragmented episodic memory representations. Interestingly, several authors have discussed how PO impairments could be a causal factor in delusion formation. For example, Turetsky et al[49] noted that reduced organization of facial features could lead to delusions involving inappropriate attribution of others' intent. Mattusek noted that attempts to account for the apparent loss of meaning during scene perception could result in delusional beliefs. In short, a still small literature suggests that PO impairments can have "downstream" consequences. Additional research is needed to clarify these relationships, however. For example, the precise contribution of reduced PO, relative to other factors, in driving impairments in emotional recognition, theory of mind, and attention and memory impairments is not yet known.

Specificity of PO Impairment to Schizophrenia

As noted in older reviews, PO impairment has been consistently demonstrated in schizophrenia, but not in other psychiatric disorders, including substance abuse disorders and psychotic disorders other than schizophrenia. Recent research is consistent with these past findings. For example, where PO impairment was found in schizophrenia, it was not found in patients with bipolar disorder,[28] psychotic disorders other than schizophrenia,[10] and patients with nonpsychotic mental disorders.[11] PO

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has also been found to be normal in people with pervasive developmental disorder,[51] including autism (even though people with autism may be better than other people at processing local detail), indicating that it is not a general correlate of abnormal brain development or severe cognitive, intellectual, or social functioning impairment.

However, PO impairment has been demonstrated in a few neurologic conditions, and these findings offer clues as to the brain mechanisms associated with the impairment in people with schizophrenia (see Silverstein[42] for review). Specifically, PO is impaired in patients with Alzheimer's disease, but only among those with white-matter abnormalities in the occipital lobe. This is consonant with the view that PO impairment in schizophrenia is due, in part, to reduced connectivity within visual processing regions.[42] In addition, human and animal studies have demonstrated that PO is impaired in amblyopia, a disorder involving abnormal development of early visual cortex integrative circuitry secondary to poor quality visual input to one eye (due to structural problems with that eye or the muscles that control it). PO impairment has also been demonstrated in patients with prefrontal (but not dorsolateral prefrontal) cortex damage and in patients with lesions to the temporal-parietal junction, consistent again with findings of reduced activity in these regions in schizophrenia patients during PO tasks. Finally, PO is reduced in people with Williams syndrome, and this finding was associated with reduced activity, as measured by fMRI, in the visual and parietal cortices (see Silverstein[42] for a review of this neuropsychological evidence).

Perceptual Organization Impairment as a Manifestation of a Widespread Reduction in Cognitive Coordination in Schizophrenia

Phillips and Silverstein[39] hypothesized that PO impairment in schizophrenia was but one manifestation of a widespread impairment in cognitive coordination—the grouping of information based on contextual relationships. In their view, this general problem could also account for failures in selective attention, lexical disambiguation, and coherent thought. They further suggested that these multiple examples of cognitive coordination failure were rooted in NMDA receptor hypofunction, with later evidence suggesting an important role also for reduced inhibitory activity of parvalbumin-containing GABA-ergic interneurons (possibly secondary to their reduced excitation via NMDA receptors but then leading to further disinhibition of excitatory activity). This would lead to failures to strengthen cell assemblies and to thereby separate contextually relevant from nonrelevant information, and to an overall increase in the salience of nonrelevant information. These failures would then generate behavior that is driven more by individual stimuli rather than by the significance of those stimuli in their current context, in multiple cognitive domains. Evidence in support of the Phillips and Silverstein[39] hypothesis includes computational models supporting a common mechanism for PO, selective attention, and lexical disambiguation in normal cognition (see online supplementary information for an annotated list of key references); theory and experimental evidence on similar computational algorithms used for perception, thought, language, and other cognitive processes (see online supplementary information); the involvement of synchronization of neural activity in PO and other cognitive processes (see online supplementary information); data from animal studies where selective activation and segregation of multiple information streams is linked to coordinated neural firing, and where pharmacologic disruption of this process occurs by weakening coupling between neurons with previously synchronized firing rates and increasing the coupling of neurons whose firing was previously independent—without affecting the firing rates of individual neurons (see online supplementary information); evidence for the role of NMDA and GABA-ergic activity in neural oscillations, and of changes in oscillations during pharmacologic manipulation of these systems (see online supplementary information); multiple examples of significant correlations between PO impairments and increased levels of disorganized (but not other) symptoms (eg, formal thought disorder) in schizophrenia (see ref. [1,30,39] for reviews, in addition to[10]); the finding that within the category of formal thought disorder, it is only loose associations and fragmented thinking (ie, examples of reduced organization in thinking), but not neologisms, novel combinations of words, or odd word usage that are associated with reductions in PO[30]; and normalization of PO during acute treatment and its association with reductions in disorganized (but not other) symptoms.[11] One way in which this is relevant is that, if indeed PO impairment is a lower level manifestation of a widespread impairment in binding, it may be useful as a biomarker of this process: it can be reliably demonstrated using brief (eg, 10 min or less), low-cost behavioral paradigms; it can be demonstrated independent of a generalized deficit; and it can be demonstrated in patients with attentional impairments and severe symptoms. This may make it useful as, for example, an early indicator of treatment response in early phase drug development studies, especially those targeting NMDA receptor and GABA-ergic functioning.

Conclusions

In the last review of PO impairment in schizophrenia, which covered studies up to 2004, it was noted that 28 of 33 studies indicated impairment and that the tendency to uncover a behavioral impairment increased to the extent that: the PO task required top-down processing, task performance depended on PO mechanisms that do not become fully mature until late adolescence or early

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adulthood, there was a history of poor premorbid social functioning among patients and there was a clinical presentation or history that included disorganized symptoms (ie, a predisposition for cognitive fragmentation during acute episodes). In the studies from 2005 to 2010 identified for this review, 25 studies demonstrated impairment, 1 EEG study demonstrated normal behavioral performance but impairments on EEG measures and 1 behavioral study indicated normal performance. Importantly, both "negative" studies have important caveats. In the first,[45] patients were nonsignificantly worse at discriminating a Kanizsa square from a fragmented control stimulus. This was likely a type II error since 2 earlier studies used virtually the same task to show that patients were slower and less accurate. However, even in the face of relatively normal behavioral performance, impairments were revealed on ERP indices. The other aberrant study[29] involved a similar benefit as controls from a reduction in distractors and could not isolate a PO impairment independent of visual attention and decision-making processes. In short, data continue to accumulate indicating PO impairment in schizophrenia and defining the task parameters within which it can be observed.

A development since the prior review is studies combining electrophysiological and/or imaging techniques (eg, EEG, MEG, fMRI) and PO tasks. These studies consistently demonstrated that PO impairment in schizophrenia is associated with disturbances in brain activity known to be associated with normal PO in healthy human samples and in animal studies. In particular, these studies point to the importance of (1) early visual cortex regions, (2) temporal lobe regions involved in object perception, (3) parietal regions involved in attention to object onsets, (4) frontal regions involved in object vision (eg, anterior portions of the ventral visual pathway), (5) the P1 and NCl components of the EEG, and (6) synchronization of oscillations within the beta and/or gamma band, depending on the nature of the stimuli (ie, depending on the cortical distance across which neural synchrony must be accomplished).

Based on a convergence of the behavioral and psychophysiological data, we conclude that there are multiple contributors to impaired PO in schizophrenia. Broadly speaking, the 2 classes of these include reduced bottom-up linking of basic features, in addition to deficient top-down feedback in the form of a reduced ability to impose structure on fragmented stimuli based on task context, expectations, and environmental regularities. Importantly, as noted in prior reviews, findings of PO impairment in schizophrenia cannot be attributed to other cognitive disturbances or to the generalized deficit. This is because in cases where stimulus grouping would interfere with task performance, patients perform better than controls overall, and even when attention to the task can be demonstrated to be normal, contour linking failures still occur. Moreover, as with studies prior to 2005, PO impairment was not found to be an artifact of antipsychotic medication. Abnormal task performance can be found in unmedicated patients,[36] and medication dose was unrelated to task performance in medicated patients (eg, ref. [13,17,26]).

Also consistent with past findings, recent studies indicate that PO impairment in schizophrenia has both trait and state aspects. Although longitudinal studies of stability over time are lacking, reduced grouping has been consistently demonstrated among nonfirst-episode schizophrenia patients (especially those with poor premorbid histories) and has been found among clinically stable relatively symptom-free patients (eg, [13]), suggesting its trait-like nature. However, repeated links between level of PO impairment and level of disorganized symptoms, higher rates of PO impairment among inpatients than outpatients,[30] and covariation of improvement in PO and disorganization during acute inpatient treatment[11] support its state-related aspects. The evidence to date therefore converges on the conclusion that PO impairment covaries with level of disorganization within a subgroup of patient characterized by poor premorbid functioning and a more severe form of illness but is still present to a higher degree than among other people even when these symptoms are in remission.

Recent studies continue to indicate that PO impairment is relatively specific to schizophrenia. It has not been found among other Axis-I disorders and is not found among people with pervasive developmental disorders.[51] However, the impairment has been demonstrated in a few specific forms of visual disturbance and brain disease, and this evidence confirms the role of specific occipital, temporal, parietal, and frontal regions, and their interaction, in the impairment.

As noted above, PO impairment in schizophrenia has now been demonstrated in many studies, and its brain bases are relatively well understood. What remains to be done are studies examining (1) its development, including whether it is present in a subgroup of patients in the prodromal stage or at first episode; (2) whether the timing of the onset of PO disturbance predicts short-term and/or long-term outcome; (3) the plasticity of the disturbance as the result of psychological and/or pharmacological interventions, and whether improvements over time are associated with change in related functions such as selective attention, working memory, face perception, social cognition, and subjective experience of the world; and (4) its genetic basis and heritability. At present, however, the wealth of available evidence suggests that PO impairment is reliably observed, can be demonstrated with a variety of brief behavioral tasks, can be demonstrated independent of a generalized deficit, is linked to severity of disorganization, and may be a low level and rather concrete

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manifestation of a more general cortical computation failure in schizophrenia involving failures in context-based modulation of feedforward activity (via both horizontal activity and re-entrant feedback, with the relative proportion of each dependent on the nature of the stimuli and task—see online supplementary information for references related to physiological mechanisms involved in PO). As such, it has the potential to serve as a biomarker of these widespread binding failures and may prove useful in intervention development studies.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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