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Early-stage visual processing deficits in schizophrenia

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Abstract

Purpose of review—While cognitive dysfunction including memory and attentional deficits are well known in schizophrenia, recent work has also shown basic sensory processing deficits. Deficits are particularly prominent in the visual system and may be related to cognitive deficits and outcome. This article reviews studies of early-stage visual processing in schizophrenia published during the past year. These studies reflect the growing interest and importance of sensory processing deficits in schizophrenia.

Recent findings—The visual system is divided into magnocellular and parvocellular pathways which project to dorsal and ventral visual areas. Recent electrophysiological and behavioral investigations have found preferential magnocellular/dorsal stream dysfunction, with some deficits in parvocellular function as well. These early-stage deficits appear to be related to higher level cognitive, social, and community function. Structural studies of occipital cortex and particularly optic radiations provide anatomical support for early visual processing dysfunction.

Summary—These findings highlight the importance of sensory processing deficits, in addition to higher cognitive dysfunction, for understanding the pathophysiology of schizophrenia. Understanding the nature of sensory processing deficits may provide insight into mechanisms of pathology in schizophrenia, such as *N*-methyl-D-aspartate dysfunction or impaired signal amplification, and could lead to treatment strategies including sensory processing rehabilitation that may improve outcome.

Keywords

magnocellular; parvocellular; schizophrenia; visual evoked potentials

Introduction

Patients with schizophrenia have severe neurophysiological deficits not only at cognitive [1-4] but also at perceptual [5-8] levels of processing. Perceptual deficits have become increasingly well documented in the visual system in schizophrenia [9-17,18•,19-21] and may contribute to higher level cognitive impairments and community outcome [12,22-24]. An early report by Saccuzzo *et al.* [25] of visual backward masking dysfunction in schizophrenia was particularly important not only because it indicated deficits in the earliest components of visual information processing [16,26,27], but also because it suggested dysfunction of a particular visual pathway – the psychophysically defined transient visual pathway [27-30].

The classic transient/sustained psychophysical dichotomy has been supplanted over recent years by anatomically and physiologically based distinctions between magnocellular and parvocellular pathways, which roughly correspond to properties of transient and sustained

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pathways, respectively. The magnocellular system, in general, conducts low-resolution visual information rapidly to cortex, and is involved in attentional capture and processing of overall stimulus organization [31-33]. The parvocellular system, in contrast, conducts high-resolution visual information to cortex, and is involved in processing of fine-grained stimulus configurations and object identification [31,34]. A focus of this review is to examine the differential functional roles of magnocellular and parvocellular systems in visual pathway dysfunction, including their contribution to 'upstream' cognitive impairments and outcome.

Both the magnocellular and parvocellular pathways begin in the retina and project, by means of the lateral geniculate nucleus (LGN), to primary visual cortex (striate cortex, V1). These pathways have very different properties, which can be manipulated to preferentially activate the magnocellular or parvocellular components of the system. For instance, magnocellular neurons are more sensitive than parvocellular neurons to low luminance contrast [35,36]. In addition, magnocellular cells are activated vigorously by stimulus elements that are relatively large, whereas parvocellular cells are activated more strongly by stimulus elements that are relatively small [37,38]. Magnocellular cells are also relatively unresponsive to chromatic (color) contrast while parvocellular cells are not [35].

Magnocellular information is conveyed preferentially to parieto-occipital cortex and other dorsal stream visual areas which are involved in motion and space perception (the 'where' pathway) [31,39]. Parvocellular information is conveyed preferentially to temporo-occipital cortex and other ventral-stream areas which are involved in color and form perception (the 'what' pathway) [31,39]. Crossover occurs at multiple levels, including from higher-order dorsal stream to higher-order ventral stream areas [40,41]. Transmission is faster through the dorsal stream, perhaps permitting it to prime ventral stream areas. A fundamental role of the magnocellular system/dorsal stream may be to 'spotlight' relevant information for transmission to ventral stream areas, so that crossover inputs from the dorsal stream may modulate activity within ventral stream structures [15,32].

In accord with the original theory of 'transient channel' dysfunction in schizophrenia, deficits are particularly prominent in processes, such as motion detection, velocity discrimination, spatial localization, trajectory, and eye-tracking tasks that depend mainly upon magnocellular input to the dorsal visual stream, and in detection of low contrast and small stimuli [9,13,14, 16,17,18•,20,42•,43,44]. However, deficits have also been observed even in processing of parvocellular-biased stimuli [20]. In addition, while some ventral stream object identification deficits have also been found, several studies provide evidence that the latter are due to aberrant crossover input from dorsal to ventral stream areas [15,19]. Advances in understanding visual processing dysfunction in schizophrenia have occurred due to use of basic neurophysiological properties of magnocellular and parvocellular neurons to selectively activate these pathways. Recent papers examining early visual processing dysfunction, with an emphasis on those related to magnocellular and parvocellular as well as dorsal and ventral stream processing, will be reviewed.

Electrophysiological studies

A primary approach to analyzing integrity of visual processing is use of visual evoked potentials (VEPs). VEPs have the advantage that they are nonbehavioral and so provide an objective measure of brain function. In particular, steady-state VEPs (ssVEPs) have been used in two recent studies [45,46]. In the ssVEP approach, stimuli are presented rapidly and may produce habituation of the higher-level cortical response and thus increase sensitivity for evaluating lower-level responses. In this approach, physical stimulus features such as luminance contrast can be manipulated to preferentially activate the magnocellular and

parvocellular components of the system. ssVEP studies provide a definitive demonstration of magnocelslular dysfunction in schizophrenia.

In one recent ssVEP study, Butler *et al.* [45] used luminance contrast to bias processing towards the magnocellular versus parvocellular pathway. In the magnocellular-selective condition, stimuli appeared and disappeared, a manipulation that preferentially engages the magnocellular system. Conversely, in the parvocellular-selective condition, stimuli were modulated around a high 48% level of luminance contrast ('pedestal') that saturates the magnocellular response, and so isolates the additional parvocellular activation [9,47]. Patients generated evoked potentials that were significantly reduced in response to magnocellular but not parvocellular-biased stimuli. In terms of the pattern of responses in the magnocellular condition, controls showed a steeply rising increase in response to low luminance contrast stimuli (~1–10% contrast) which reached a saturation level once luminance contrast reached ~16–32%, similar to what is seen in single-cell recordings from magnocellular neurons in monkey LGN [35]. However, responses of patients showed a much shallower gain at low luminance contrast and a much lower plateau. Visual pathways within the brain use glutamate as their primary neurotransmitter. The decreased contrast gain and plateau in the magnocellular-biased ssVEP contrast response curve for schizophrenia patients in this study closely resembles results seen following microinfusion of an *N*-methyl-D-aspartate (NDMA) antagonist into cat LGN and visual cortex [48,49], consistent with glutamatergic theories of schizophrenia [50-52]. ssVEP m easures also predicted community functioning.

In a second ssVEP study, Kim *et al.* [46] utilized windmill–dartboard and partial-windmill stimuli to investigate responses across harmonic levels (Fig. 1). In most studies utilizing ssVEPs, the first harmonic response, extracted by Fourier transform, is used to analyze data. The first harmonic refers to responses at the stimulus input frequency. However, second harmonic responses can also be extracted. The second harmonic refers to responses at twice the stimulus input frequency. The windmill–dartboard condition used in this study produces ssVEP responses with a dominant first harmonic and an attenuated second harmonic, whereas the partial-windmill condition produces an ssVEP that contains a dominant second harmonic response. Second harmonic responses are preferentially elicited by achromatic [53] and low spatial frequency [54,55] stimuli and are thus thought to be mediated primarily by magnocellular system activity. In contrast, first harmonic responses are elicited by contrast above the magnocellular-specific range of function [56], which indicates a dominant role of the parvocellular pathway in the generation of the first harmonic [57]. Schizophrenia patients showed reduced amplitude and coherence of second harmonic responses in both conditions, but intact first harmonic responses in the windmill–dartboard condition (Fig. 2). This indicates a significant loss in the magnocellular pathway, which contributes to the generation of the second harmonic component under these conditions.

During the past year transient VEP studies also addressed early visual cortical responses in schizophrenia. In this approach, stimuli are presented more slowly and responses are analyzed in the time domain. Butler *et al.* [58] reported decreased amplitude of the P1 component, consistent with the earlier findings of Doniger *et al.* [15]. In addition, Haenschel *et al.* [59] reported decreased P1 amplitude in patients with early-onset schizophrenia. In contrast, van der Stelt *et al.* [60] did not find decreased P1 or N1 in schizophrenia.

Thus, ssVEP studies provide strong evidence of magnocellular dysfunction in schizophrenia, and transient VEP studies, in general, support early visual cortical dysfunction.

Behavioral studies

Visual pathway function has also been studied using behavioral methods. While studies using luminance and chromatic contrast to bias processing towards magnocellular and parvocellular

pathways have generally shown preferential magnocellular dysfunction, studies utilizing stimulus size to bias processing have been more equivocal. The latter studies assess the amount of contrast (i.e. contrast threshold) needed to detect stimuli of varying sizes with large (i.e. low spatial frequency) stimuli biasing processing towards the magnocellular pathway and small (i.e. high spatial frequency) stimuli biasing processing towards the parvocellular pathway. Lower thresholds indicate better performance. One issue is that high spatial frequency stimuli can produce low contrast thresholds. Because the magnocellular system responds well to low luminance contrast (~1–10% contrast), whereas parvocellular neurons do not start responding until stimuli reach higher contrast (~10%), contrast threshold levels below 10% will be biased toward the magnocellular system regardless of spatial frequency. In addition, responses to spatial frequency are not specific to striate versus extrastriate areas [39].

Several studies in the last year have used contrast to examine magnocellular and parvocellular function. Using a backward masking paradigm, Schechter *et al.* [18•] used low luminance contrast to bias processing towards the magnocellular system and chromatic contrast at isoluminance to bias processing towards the parvocellular system. Backward masking dysfunction was found when low luminance but not chromatic contrast stimuli were used as masks, supporting a role of magnocellular-system dysfunction in backward masking deficits in schizophrenia. In a vernier acuity task, Keri *et al.* [61••] used low contrast and low spatial frequency to bias processing towards the magnocellular system and high contrast and chromatic contrast at isoluminance to bias processing towards the parvocellular system. Patients showed deficits in vernier acuity in the low spatial frequency and low contrast conditions, but not in the high contrast and isoluminant color contrast conditions, consistent with magnocellular dysfunction. In a far-out jerk paradigm, Slaghuis and Thompson [62•] examined the ability of moving objects in the periphery to decrease detection of a central object. The far-out jerk response is thought to be mediated by long-range transient or magnocellular function. Patients with predominantly negative, rather than positive, symptoms of schizophrenia showed a decreased far-out jerk response, indicating magnocellular dysfunction.

Most backward masking studies in schizophrenia have been done using masks that spatially overlap the targets [13,26,63-65]. Rassovsky *et al.* [66] recently examined masking in schizophrenia using masks that surround, rather than overlap, the target. This technique limits the mechanism of masking to interruption. Patients with schizophrenia showed deficits in masking by interruption, consistent with magnocellular dysfunction [16,28].

While studies within the past year using stimulus size to bias processing have consistently found contrast threshold deficits to low spatial frequency stimuli, reflecting magnocellular dysfunction [42•,45,62•,67•], results are less clear at medium to higher spatial frequencies. Slaghuis [62•,67•] reported a threshold detection deficit at medium and higher spatial frequencies of 4 and 8 c deg^{-1}, indicative of parvocellular dysfunction. Butler *et al.* [45], however, reported a deficit at spatial frequencies up to 7 c deg^{-1} but not at higher spatial frequencies of 10 and 21 c deg^{-1}, suggesting intact parvocellular function. Differences in absolute contrast levels at medium and high spatial frequencies may underlie variant findings.

Contrast detection has also been utilized to examine whether visual processing deficits are related to early-stage processing dysfunction. Slaghuis [67•] found that backward masking dysfunction was related to deficits in contrast threshold, which supports a role of early-stage visual processing deficits in backward masking dysfunction in schizophrenia. They commented that an earlier study by Keri *et al.* [68] did not find such a relationship, which may have been due to measurement of contrast thresholds in central vision and backward masking in four separate parafoveal locations in that study, whereas Slaghuis [67•] measured both in the same central retinal location.

Chen and colleagues have found motion processing deficits in schizophrenia as seen in impaired velocity discrimination [14,42•,69] and have also used contrast to examine whether this deficit is intrinsic to dorsal stream motion areas or due to impaired early-stage input [42•]. They pointed out that neurophysiological and lesion studies show that a velocity discrimination deficit may be related to early-stage motion processing (i.e. LGN, striate cortex) if it is contrast dependent and later stage processing (i.e. extra-striate) if it is contrast independent. Thus, they assessed velocity discrimination at high and low contrast, using each participant's contrast detection threshold to equate contrast levels. Patients showed impaired velocity discrimination that did not improve with high contrast, whereas performance of controls did improve with increased contrast. The contrast independence of the deficit in schizophrenia indicates that it is mediated by later-stage extra-striate areas.

With regard to effects on higher level function, contrast threshold deficits were found to be related to impaired neuropsychological as well as community function [45], reminiscent of findings by Gold *et al.* [22]. Furthermore, backward masking deficits are related to impaired social perception [24].

In addition to deficits in visual pathway function in schizophrenia, there may also be abnormal lateral interactions in visual cortex in schizophrenia [70].

Medication effects

An unresolved issue is the degree to which medication may affect visual processing. Chen *et al.* [71•] have suggested that decreased contrast detection thresholds are related to medication such that they are found only in patients taking typical, rather than atypical, antipsychotics. In other studies, however, ssVEP and contrast detection thresholds as well as visual masking dysfunction were observed even in patients receiving atypical antipsychotics alone [45,66], suggesting that patient characteristics rather than medication type may be the primary predictor of visual dysfunction. In addition, decreased magnocellular-biased vernier acuity as well as aberrant lateral interactions were found in patients who had been off medications for several weeks [61••,70].

Patient characteristics

Several recent studies have examined early visual processing in various groups of participants. Within schizophrenia groups, Slaghuis [62•,67•] found that deficits in contrast detection, backward masking, and far-out jerk tasks are more prominent in patients with predominantly negative, rather than positive, symptoms of schizophrenia. Rund *et al.* [64] reported that patients with schizophrenia, but not unipolar depression, show impaired backward masking compared with controls and concluded that backward masking is a sensitive measure of the visual processing dysfunction in schizophrenia. Decreased magnocellular-mediated vernier acuity has also been found in first-degree relatives of patients with schizophrenia [61••], as has decreased magnocellular/dorsal stream function using functional magnetic resonance imaging (MRI) [72], suggesting that early visual processing deficits may be a possible endophenotype.

Anatomical studies

Inputs to primary visual cortex project from LGN to V1 via optic radiations. These white matter tracts can be examined by MRI using the technique of diffusion tensor imaging. Recently, decreased integrity of occipital white matter adjacent to the corpus callosum, in the region of the optic radiations, has been found in adults with schizophrenia [73•], in agreement with an earlier study [74]. Decreased occipital white matter integrity has also been found in adolescents with early onset schizophrenia [75•]. In addition, a significant relationship has been found between decreased magnocellular-biased ssVEP responses and decreased white matter

integrity in the optic radiations, but not in higher level visual areas [45] (Fig. 3). The latter finding provides direct support for the hypothesis that magnocellular dysfunction occurs at the earliest stages of visual responsivity.

Conclusion

Results from behavioral and electrophysiological studies support early visual processing dysfunction in schizophrenia, with preferential deficits being found in the magnocellular pathway, though parvocellular deficits have been found as well. Preferential magnocellular dysfunction may provide a substrate for dorsal stream dysfunction as well as higher level cognition deficits and outcome. Structural deficits in occipital cortex, particularly in optic radiations, and their relationship to early visual processing deficits, document the importance of subcortical as well as cortical dysfunction in schizophrenia.

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Abbreviations

LGN
: lateral geniculate nucleus

ssVEP
: steady-state visual evoked potential

VEP
: visual evoked potential

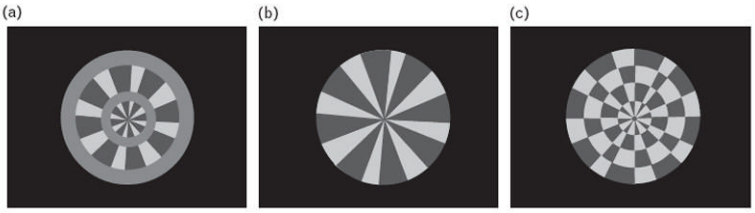

Figure 1. Partial-windmill and windmill–dartboard conditions

(a) The partial-windmill condition. The pattern elements in the central disk and second annulus contrast reverse to produce a partial windmill. (b, c) Windmill–dartboard condition. The windmill–dartboard stimulus has two distinct phases: windmill, shown in (b), and dartboard, shown in (c). The contrast of the first and third annuli are held constant. Contrast reversal of the pattern elements in the central disk and second annulus result in the change of appearance from a windmill to a dartboard. Reprinted with permission from Elsevier [46].

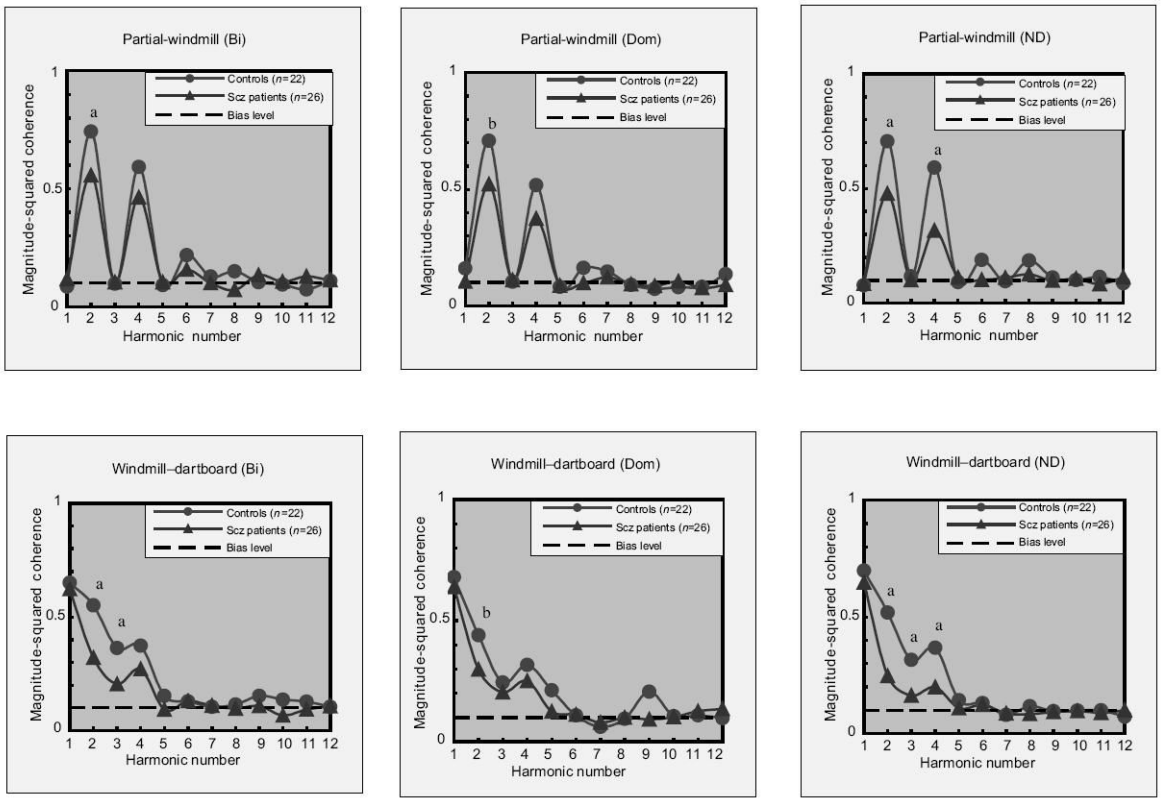

Figure 2. Partial-windmill and windmill–dartboard conditions

Patients with schizophrenia (Scz) showed significantly reduced second harmonic responses but intact first harmonic responses. This finding of a differential deficit may indicate a significant loss in the magnocellular pathway. Bi, binocular eye condition; DO, dominant eye condition; ND, nondominant eye condition. a, $P < 0.01$; b, $P < 0.05$. Reprinted with permission from Elsevier [46].

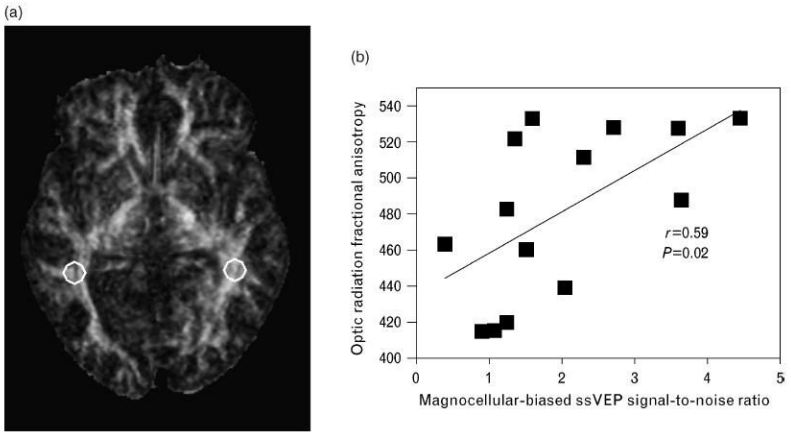

Figure 3. Fractional anisotropy (FA) image and scatter plot

(a) FA image with circles representing regions of interest based on their placement in the optic radiations on the $b = 0$ image (not shown). (b) Scatter plot showing relationship between magnocellular-biased steady-state visual evoked potential (ssVEP) responses and FA of optic radiation white matter tracts for patients with schizophrenia. FA measures range from 0 to 1 with 0 representing complete isotropic diffusion (no directional selectivity of water diffusion and hence decreased white matter integrity) and 1 representing complete anisotropy. FA values have been multiplied by 1000. Reprinted with permission from Elsevier [45].