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NEUROPHYSIOLOGIC MECHANISMS OF ATTENTION: A SELECTIVE REVIEW OF EARLY INFORMATION PROCESSING IN SCHIZOPHRENICS

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1. ABSTRACT

Attention is an integral component of information processing. A pronounced attention deficit exists among people with schizophrenia and their first-degree relatives as compared to persons without this pathology. Schizophrenics demonstrate marked deficiencies on psychophysical tasks that require temporal and / or spatial integration, properties that are associated with the two primary visual pathways composed of magnocellular (M) and parvocellular (P) cells, respectively. The deficit expresses itself as a dysfunctional information processing system that affects higher order processes, for example, perceptual ability and memory. The focus of this review is to integrate results from several divergent areas of research to include those studies that identify the contributions of the M and P pathways associated with information processing and the attention deficit. The diverse approaches reviewed in this chapter converge to provide a neurophysiologic explanation of the attention deficit in schizophrenia.

2. INTRODUCTION

Throughout the history of experimental psychology attention has been used to assess the core cognitive processes. Attention research intensified after the publication of Broadbent's book, *Perception and Communication* (1); however, despite a significant quantity of research on attention, its definition remains obscure (2). Holzman, *et al* (1978) proposed that processes such as (visual) anticipating, searching and selecting, activation, concentration, and / or alerting are integral components that contribute to the operational definition of attention (3). Since attention facilitates the flow of information processing, it follows that a disruption in the attention system disturbs the continuity of information processing. Identifying the normal functional status of each attention process affords the opportunity to accurately index the role of attention in behavioral, psychologic, and neuropsychologic areas with respect to different clinical populations including schizophrenia.

Schizophrenia is a severe and chronically debilitating disease with profound psychosocial consequences. The DSM-IV (4) outlines two categories of symptoms that characterize schizophrenia: positive and negative symptoms. Positive symptoms consist of delusions, hallucinations, disorganized speech, and grossly disorganized or abnormal thinking and behavior, while affective flattening, alogia, and avolition comprise negative symptoms. These symptoms must persist for a period of 1 month with continuous signs of the disturbance(s) persisting for a minimum of 6 months. The more debilitating symptoms of schizophrenia, however, are disturbances in attention and cognition, which were observed as early as the 1900s by Kraeplin (5).

Various laboratories have endeavored to identify the pathophysiologic mechanisms underlying the cognition and attention deficits within schizophrenia. Our research and that of others attempts to further our understanding of schizophrenia by advancing the understanding of the neurophysiologic and neuroanatomic mechanisms of attention / information processing. This chapter samples the diverse research approaches and their results that oftentimes converge to provide a neurophysiologic explanation of the attention deficit in schizophrenia.

Table 1 Differences between Parvocellular and Magnocellular pathways

	Parvocellular	**Magnocellular**
Response Characteristics	sustained	transient
Receptive Field Size	small	large
Stimulus Onsets and Offsets	-	+
Motion	-	+
Color	+	-
High Spatial Frequency	+	-
Low Spatial Frequency	-	+
Response Latency	long	short
Conduction Time	slow	fast
(+) maximal response		
(-) minimal response		

3.1. Attention and Cognition

Posner and Peterson (1990) (6) posit that attention consists of three subsystems: (1) visual orienting to sensory events, (2) target detection for conscious processing, and (3) the alerting or vigilance system which maintains attention functions for the processing of high priority signals. Another way of conceptualizing attention is in terms of preattentive and attentive stages. Preattentive mechanisms operate in parallel and are unlimited in capacity, while the attentive mechanism operates serially and restricts attention to one location at a time. For example, on visual search tasks, search times are independent of array size when the target differs by a single feature while search times are highly dependent on array size when the target shares a common feature with the other array elements. The preattentive stage is often conceptualized as an automatic reflexive/ sensory mechanism and the attentive stage as volitional and cognitive (7.8). From a neurophysiologic standpoint, pre-attentive processes result primarily from bottom-up or more stimulus driven mechanisms (sensory events) while attentive processes are mediated by top-down, or mechanisms that require cognitive involvement / activation (9,10)

The ability to select and respond to stimuli is subject to both internal and external control. Sudden motion or noise in our peripheral surroundings can cause an "automatic" or involuntary orienting of attention to the external events (8). Voluntary control of attention is associated with internal control or conscious decision-making and it is termed *endogenous*, while the involuntary movement of attention in response to an external event is termed *exogenous* (11). When the eyes remain stationary the movement of attention is referred to as "covert" attention (i.e., without eye movement).

3.2. Visual Pathways Model

A parallel visual pathways model (12) identifies spatial and temporal properties of stimuli that can selectively activate two primary spatial and temporal neurophysiologic pathways. The two visual pathways are anatomically defined as: magnocellular (M) and parvocellular (P). These pathways remain relatively segregated as they project (in parallel) (13) from the retina through subcortical and cortical visual loci. The M pathway is subserved by large receptive field cells analogous to "Y" cells, identified in animal studies (14). "Y" type cells are located throughout the retina and are primarily responsive to briefly presented, low spatial frequency visual information. One of their functions is to orient attention to the *appearance* or *presence* (i.e., "where is it") of stimuli. Cells within the M pathway respond with a sudden burst of activity to stimulus onset and, therefore, are referred to as *transient type cells* that constitute the *transient pathway or channel.* In contrast, the parvocellular (P) pathway is composed of the smaller receptive field cells equivalent to "X" cells. These cells are located in or near the fovea. The primary function of the P pathway is *identification* and object *recognition* (i.e., "what is it"). "X"- type cells are primarily responsive to high spatial frequency information and respond with long response latency and a slower rise time. Psychophysically the M and P pathways are conceptualized as transient and sustained channels, respectively (15-17) (Refer to Table 1). Although a one-to-one relationship has not been established between the electrophysiologically /anatomically defined M and P neurons with the psychophysically defined transient and sustained channels, the terminology is often applied interchangeably.

In normals, visual information processing and attention at subcortical and cortical levels can be classified by M and P response profiles to spatial frequency, temporal frequency, contrast and color (13, 18-26). Although there is some overlap in their characteristic response properties, the M pathway is primarily involved in detecting motion, depth, localizing visual objects, and processing coarse form; the P pathway processes pattern information (i.e., fine form) and color but not much depth or motion (21,22). The anatomical segregation of the two pathways begins at the retina, continues through the lateral geniculate nucleus of the thalamus, through cortical area V1 and V2, and at least up to areas V4 and V5. The functional segregation of the two pathways after area V1 continues to be debated.

Preattentive and attentive processes can be further ascribed to subcortical and cortical areas, respectively (6, 27). At the level of the cortex, this division corresponds to the dorsal (parietal) and ventral (inferotemporal) streams (28), where parietal areas receive input primarily from the M pathway and temporal areas receive both P and M input (29). The projection patterns from the retina to the superior colliculus (SC) receive extensive input from the M cells, but not from P cells that regulate color-opponent processing. Neurons in the extrastriate M pathway processes motion while the P pathway processes color and form information. M neurons show poor color selectivity, thus it is implied that a pure chromatic contrast invisible to M cells will also be invisible to the motion pathway (30, 31). That is, when a stimulus is defined solely by color contrast, M pathway activity is diminished and task performance primarily indexes P activity. A number of studies have identified cortical areas MT and V4 as selective for motion and color respectively. Findings support the segregation of motion and color information and favor a parallel processing scheme. For instance, motion perception is impaired for isoluminant stimuli, which are defined solely by color contrast.

3.3. Theories / Models of Attention

A brief selected review of normative theoretical models will provide the foundation for their application to schizophrenic information / attention processing. Posner, et al's (1984) (32) model of attention proposes three processes involved in the shifting of covert attention from one source to another: (1) disengaging attention from its current focus, (2) moving attention to the target, and (3) engaging attention to the target. Difficulties disengaging attention are observed after parietal lesions while deficits in the shifting of attention are noted after degeneration of the superior colliculus (33). Furthermore, impairments in any one of these functions could produce an overall impairment in attention. For example, in an exogenous cueing paradigm, a cue (e.g., brightening of a peripheral square) precedes the onset of a peripheral target (e.g., asterisk presented within a square) either at the target location (valid) or at a different location (invalid). Valid cues are associated with faster manual reaction time (RT) whereas invalid cues are associated with slower manual reaction time in comparison with a no-cue condition. With long cue-to-target delays reaction time (RT) is slowed. This is termed inhibition of return (IOR) and reflects inhibition to previously attended locations. In the valid condition, attention is disengaged automatically and moved to the target location prior to the target onset, while in the invalid condition attention is disengaged volitionally from the cue and then moves to the target. The reaction time difference is the time required to perform the additional mental operations associated with the invalid condition. In the endogenous paradigm, the cue is presented at a central location and it provides a symbolic meaning (e.g., the words "left" or "right" or an arrow pointing to the left or right) as to the impending location of the target.

The disengage, move and re-engage operation of attention is thought to be linked closely with overt eye movements (34). Many of the same regions implicated in attention are also involved in the generation of eye movements (e.g., the superior colliculus (SC), frontal eye field (FEF), intra-parietal sulcus, and thalamus). In this regard, the premotor theory of attention proposes that shifts of attention and eye movements (i.e., motor preparation) result from neural activity within the same regions (35, 36). Rosen *et al.* (1999) (34) offer support for this theory in their observation of premotor area activation on both endogenous and exogenous attention conditions.

Various theoretical models have been proposed to describe how attention acts selectively to enhance elements of the visual scene. Saliency map based models (37) suggest that stimulus features compete at the neuronal level resulting in a winning location for the focus of attention (38). In Itti and Koch's model (2000) (38) inhibition of return (IOR) (i.e., inhibition to a previously attended location) provides a mechanism whereby visual search is accomplished by bottom-up, stimulus driven mechanisms (e.g. preattentive). A failure of IOR would result in the inability to proceed to the next most salient object. Top-down, attentive mechanisms, may operate to enhance the visual filter, for example, elements that selectively respond to stimulus features such as orientation or shape (39).

Leberge's (1997) (40) model is based on the selective enhancement of cortical columns. In this model, a prefrontal cortical area connects to a cortical region (e.g., the posterior parietal cortex for object localization) directly and indirectly via the thalamus (triangular circuit). The direct pathway selects which cortical column is activated while the thalamic route acts to amplify or intensify activity within the column. Other such triangular circuits (e.g., between the posterior parietal and V4) could then signal location information from the dorsal pathway to the ventral pathway to select a segment of the visual scene.

Vidyasagar (1999) (41) proposed a model of attention that incorporates the known response properties of the magnocellular (M) and parvocellular (P) pathways. The model is based upon the observed latency advantage (i.e., faster conduction) associated with the dorsal visual pathway as compared to the ventral pathway (42). In this model, the faster conducting dorsal pathway is proposed to feedback to earlier stages in the visual pathway and thus facilitates processing in the ventral stream (i.e., attention spotlight). This is supported by the observation that cells in V1are modulated by attention only after approximately 100 msec following stimulus onset (43). Consequently, parvocellular deficits as well as cognitive dysfunction are possible secondary to the failure of initial or early magnocellular modulation.

The parallel visual pathway model, therefore, provides a parsimonious neurophysiologic explanation of the attention and cognitive deficit in schizophrenia (44, 45). Consequently, Schwartz and colleague's focus is primarily on the preattentive level of processing in schizophrenics since deficits at this level are believed to adversely affect later / higher order attention processes.

3.4. Measures of attention

Individuals with schizophrenia often display a general problem in engaging and / or allocating sufficient information processing capacity: the ability to merge (cognitive) resources together at any given moment to perform specific (cognitive) tasks (46). This includes a prominent and generalized deficit in the ability to allocate and sustain attention. To this end, researchers have utilized a broad range of indices from experimental psychology laboratories to examine information processing and attention in individuals with schizophrenia. These indices include (1) critical stimulus duration (47, 48), (2) visual masking (12, 15, 18, 49-52,53-62), (3) the continuous performance task (CPT) (63-70), (4) pre-pulse inhibition (71-75), (5) eye movement tasks (2, 76-83) to include: (5a) smooth pursuit (84-91), (5b) saccade tasks (78, 92-98), and (6) visible persistence (44, 99). Interpretation and comparison of these results converge to reveal a deficit in the schizophrenic's ability to allocate attention within the first hundred milliseconds after stimulus presentation. This provides support to the time sensitive (temporal) model associated with the preattentive stage of attention that has proven deficient in patients with schizophrenia (44).

Early studies by Schwartz, *et al* (1982) (44) indirectly investigated the neurophysiologic basis of the schizophrenia attention deficit that included the evaluation

of the *temporal* aspects of preattentive visual processing in unmedicated acute and chronic schizophrenics. This study used basic stimuli, e.g., sine-wave gratings, in order to differentially stimulate the parallel visual pathways. Findings indicated that both groups required longer inter-stimulus intervals (ISI's) than controls, with chronic schizophrenics performing poorest to detect sequential presentations of stimuli that were designed to selectively activate the magnocellular pathway. This finding suggested either abnormal visual pathway activity or a dysfunction in inhibitory mechanisms between the pathways that prevented the termination of visible persistence.

Through the use of various psychophysical tasks, research by our laboratory (100-101) and those of others have attempted to evaluate the independent contributions of the M and P pathways to attention and information processing. The intention of such tasks is typically to functionally lesion either pathway by utilizing stimuli that would maximally facilitate their separation. More specifically we endeavor to study the underlying neurophysiologic mechanisms associated with information processing deficits with respect to attention by "teasing out" the contributions of the respective M and P pathways. Generally, transient cells (of the magnocellular pathway) are responsible for early stimulus detection and gross recognition of overall form (i.e., low spatial frequency information) while sustained cells (of the parvocellular pathway) are utilized primarily in object recognition (i.e., fine detail composed of high spatial frequency information). Visual backward masking (VBM) is one paradigm that is used often to dissect and isolate the variable components of the (dysfunctional) attentional / information processing system associated with schizophrenia disorder (102).

3.4.1. Visual Backward Masking

In visual masking, a briefly presented target (usually a letter) is followed by a variable duration inter-stimulus interval (ISI) and then by a masking stimulus (e.g. noise pattern). Because the mask is presented after the target, the procedure is called visual backward masking (VBM), i.e., the mask acts backward to interfere with the processing of the target. The ISI serves as an estimate of the interval of time necessary to process the (target) information. The backward masking paradigm has been utilized extensively because it provides a measure of the earliest stages of attention / information processing and it emphasizes a crucial time-dependent attention mechanism.

Visual masking paradigms (53-56, 103) reveal that schizophrenics are deficient in processing rapidly presented sequential information. Subsequent studies reveal that a decrease in processing efficiency is restricted within a temporal window of 70 to 120 milliseconds for schizophrenics; a finding supported by numerous studies including Patterson et al, (1986) (104). The results were interpreted as indexing a deficient fast, transient-like preattentive processing component in schizophrenics.

To further explore the temporal and spatial processing by schizophrenics, Schwartz *et al.* (1988b), utilized a two-pulse temporal resolution paradigm (103). The dependent measure of this task was the temporal interval in milliseconds at which two briefly presented spatial frequency patterns can be just noticeably seen as discontinuous patterns. Schizophrenics were deficient in their ability to detect and temporally resolve changes between 3.25 and 6.5 Hz, an observation recently supported by Slaghuis & Bakker (1995) (53).

It is reported extensively that schizophrenics display a selective impairment on backward masking (15,18, 20, 47, 50, 57-59, 105-109). This pattern of findings implicates aberrant M pathway function at the preattentive stage of processing for schizophrenics (44), either as abnormal activation of the M pathway (i.e., transient on transient activity) or by its interaction with the P pathway (i.e., transient on sustained). The transient - sustained interaction indexes an inefficient processing of spatio -temporal events. Support for an M abnormality at the preattentive stage of processing in schizophrenics is available from Merritt and Balogh (1989) (51), Schuck and Lee (1989) (52), and Braff *et al* (1991) (102). These studies suggest that the information processing and attention deficits in schizophrenia are secondary to a neurophysiologic pathway dysfunction.

In this regard, the transient channel is characterized by an abrupt onset and offset activation to visual stimulation, and responds optimally to low spatial and high temporal frequencies, whereas, a sustained channel response is characterized by a gradual onset activity and responds optimally to high spatial and low temporal frequencies (Refer to Table 1). When two stimuli are sequentially presented the interplay between these two channels is such that the abrupt onset of the transient activity produced by the second stimulus (e.g., mask) acts to inhibit the slower sustained activity produced by that same stimulus. The result is a termination of the temporal integration epoch or visible persistence. Visible persistence is the length of time that a visual stimulus remains visible after its physical termination. The duration of visible persistence is the minimum temporal separation between stimulus events allowing for detection of the spatio-temporal separation (i.e., termination of sustained activity).

To assess visible persistence decay rates for schizophrenics and substance abusers, Schwartz *et al* (1994) (19) utilized a two-pulse forced choice information-processing task that consisted of three stages. Two spatial frequency gratings were presented sequentially with grating pulse duration of 150msec separated by an interstimulus interval (ISI) of variable duration (30 to 350 msec). The ISI was either a blank field or a single vertical bar that appeared in the same spatial position as the center most bar of the spatial frequency grating. Participants responded "yes" or "no" if they did or did not see the bar. The task's dependent measure was the number of correct detections of the bar and the blank ISI. Schizophrenics displayed a persistent inability to detect the bar, an observation which signifies that the spatial frequency grating persisted throughout the ISI. Schwartz *et al.* concluded that the termination of visible persistence is regulated for normal controls and depressed controls by the interplay of transient

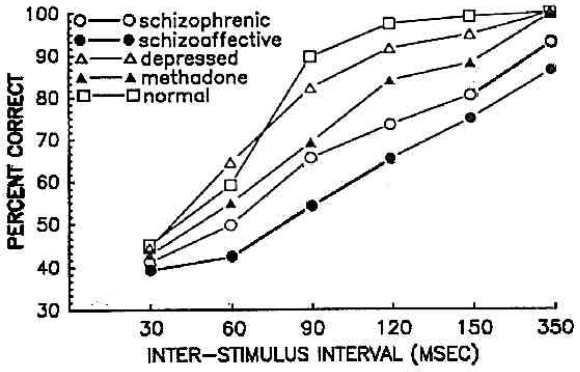

Figure 1. Decay of visible persistence for each group as indexed by percentage of correct line detections across interstimulus intervals> (SDs averaged across the low and high spatial frequencies for the 90, 120, and 150 msec ISIs for each group were as follows: schizophrenic = 25.4; schizoaffective = 22.3; depressed = 18.2; methadone = 24.6; and normals = 6.1

and sustained activity, whereas for schizophrenics and substance abusers the termination of visible persistence occurs primarily by the gradual decline of minimally inhibited sustained activity (i.e., a failure of inhibition of sustained activity by transient activity) (see Figure 1). It was also theorized that the findings indicated a potential role for abnormal dopamine transmission at the level of the retina in schizophrenia. Recently, on two apparent motion tasks, one requiring the detection of small displacements of low contrast vertical bars and the second an estimation of the visible persistence of moving dots, Tassinari et al., (1999) (110) observed prolonged visible persistence in patients with compression of the M- subcortical pathway. Several mechanisms can account for masking and visible persistence deficits in schizophrenics. Inter-channel inhibition, or masking by interruption occurs when the transient activity associated with the mask inhibits the sustained activity of the target prior to target identification. Another possibility is that sustained activity from the mask integrates with the sustained activity of the target (i.e., intra-channel inhibition). The results from the Tassinarri study (110) support the above hypothesis in that patients who suffer from a compression deficit are less sensitive to the inhibitory signals that suppress visible persistence, a finding that further implicates and supports selective impairment in the M system in schizophrenia.

Green, Nuechterlein, and Mintz (1994ab) (54, 55) observed a deficit in schizophrenics' ability to identify "blurred targets" on a visual backward masking task. They utilized two task manipulations to emphasize transient channel function: 1) the target was blurred thereby lowering the spatial frequency and 2) the subjects were required to localize the target, a function (i.e., target localization) that relies primarily upon the transient or magnocellular pathway. Their results suggested that schizophrenic deficits resulted from masking by interruption. That is, overactive transient activity associated with the mask interfered with target processing.

Saccuzzo *et al.* (1996) (59) assessed forward (i.e., when the mask precedes the target) and backward masking performance in schizophrenics. It is believed that forward masking assesses peripheral processes whereas backward masking is mediated by central mechanisms thereby differentiating the status of peripheral (i.e., subcortical) versus central masking mechanisms, respectively. On a two-alternative forced choice task participants were asked to identify the position of the target (either up or down). The mask stimuli, consisting of "V"s and "W"s presented in a four-field tachistoscope, completely superimposed the target rendering it unrecognizable during simultaneous presentations. Schizophrenics displayed a selective deficit on the backward masking condition leading to the conclusion that central processes mediate schizophrenic deficits.

Suslow and Arolt (1998) (60), used a backward masking task with blurred letters as targets, fixed ISIs of 14.3, 42.9, and 114.4 msec, and random noise (i.e., groups of letters) as the masking conditions, revealed impaired performance for schizophrenics at ISI's of 43 msec and 114 msec. Interestingly, both normal controls and individuals with depression improved performance over blocks at ISI's of 114 msec, while the performance of schizophrenics remained stable or diminished (see also Saccuzzo and Braff, 1981 (107)). The performance improvement by normals and depressives is proposed to reflect top-down attentional strategies. Thus, performance on the backward masking task may index early sensory processing and also later attentive mechanisms. Following these results, it appears that the schizophrenic deficit involves an early sensory component, and a subsequent failure to mobilize volitional attention in order to enhance target processing.

Differential deficits are associated within particular diagnoses as VBM deficits are noted more predominantly in negative-symptom schizophrenics (i.e., characterized by a marked reduction in emotional responses) than in positive-symptom schizophrenics (58, 102). This finding is further supported by Slaghuis (1998) (111) who, on a spatial frequency grating paradigm, observed diminished performance by negative symptom schizophrenics as opposed to schizophrenics with predominantly positive symptoms. Additionally, masking deficits are present in first-degree relatives of schizophrenics (75, 89) as well as schizophrenia spectrum individuals (51) suggesting that masking deficits indexes an underlying neurophysiologic abnormality. In this regard, Green *et al.* (1997) (56), utilizing a backward masking task, observed both an early sensory and later attentional disengagement deficit for schizophrenics whereas their relatives displayed a dysfunction only on the early sensory component. These findings lend further support to the growing argument for the utilization of psychophysical tasks (such as backward masking and visible persistence) as a phenotypic marker.

In summary, results from visual backward masking and visible persistence studies suggest that schizophrenic's information processing deficits are associated with a dysfunction of a fast, transient-like

mechanism. Accordingly, dysfunction in transient pathway function may be reflected in deficits in higher order tasks that are dependent on this pathway for initiating the early allocation of attention. Important consideration for future research include controlling stimulus parameters (e.g., spatial frequency, chromaticity, luminance, and exposure duration) that can optimally define the relative contribution of transient and/or sustained channels to the schizophrenic deficit.

In this regard, the VBM is an extensively used paradigm that provides an approximation as to the underlying neurophysiologic substrate regulating attention/ information processing. However, it is believed that use of letters makes visual channel interactions more difficult to explain in comparison to the use of a single homogenous target. That is, using letters as targets is problematic in that they may be differentially recognizable and confusable (53). Therein lies the rationale for the use of spatial frequencies to identify the neurophysiologic and functional status of the visual system and its response properties (52, 53, 61, 111). Essentially, one can argue that the use of letters as target stimuli has limited the explanatory domain of masking studies in schizophrenia.

3.4.2. Saccadic Eye Movement

Evaluation of saccadic eye movement provides a further means to assess attention and information processing in schizophrenia. Saccadic eye movements are short duration and high velocity ballistic eye movements that direct the fovea across a visual scene (112). Saccadic eye movements and covert shifts of attention are proposed to be closely linked and to occur in parallel: the disengage, move, and re-engage system of covert attention precedes saccadic eye movements. The relationship between saccades and attention is available from studies that have manipulated the temporal relationship between the fixation's offset and the target's onset (96, 113, 114).

During a typical reflexive paradigm, the subject initially fixates to a central point and then re-fixates to the onset of a peripherally appearing target. The central fixation is generally offset at target onset. Saccade latencies are defined as the time from target appearance to the initiation of eye movement. Investigators have observed that schizophrenics have normal saccade latencies on standard saccade tasks (78, 79, 115). Conversely, the antisaccade task requires subjects to execute a saccade to the opposite direction as the peripheral stimulus. During this task schizophrenics have consistently failed to inhibit reflexive saccades to the target.

The *Gap* and *Overlap* conditions are variations from the standard reflexive paradigms that provide additional quantification of fixation / attention mechanisms. On the gap condition the central fixation is removed before the onset of the target, whereas on the overlap condition the central fixation remains on after the onset of the target (94, 95, 113). On the gap condition saccade latencies decrease while on the overlap condition saccade latencies increase. The latency difference between gap and overlap conditions identifies the time required to disengage attention from fixation (95, 113, 116). The latency difference is partially accounted for by the early termination of fixation stimulus during the Gap condition that affords unimpeded disengagement and movement of attention to the target in the absence of fixation. In contrast, the overlap condition requires additional latency, as attention must first disengage from fixation before moving to the target.

Evans and Schwartz (1997) observed that schizophrenics required an increase in saccade latency to gap and overlap fixation conditions that was specific to the left visual field (98-100). The deficit was largely independent of fixation condition (e.g., gap versus overlap), however was most pronounced in the overlap condition (i.e., in the presence of fixation). These results were interpreted as either an asymmetry of inhibitory processes in the SC (e.g., between SC cells involved in fixation and saccades) or as a deficient alerting mechanism. Parenthetically the right hemisphere is involved in maintaining an alert state (117). In the gap condition, the offset of the fixation prior to target onset alerts the observe to impending change that is not provided in the overlap condition (see Reuter-Lorenz et al., 1995 (118)). The alerting component, along with attention disengagement is a likely explanation for the latency advantage in the gap condition. Other studies reveal that patients with schizophrenia have greater saccade latency facilitation when fixation offset preceded target onset (i.e., a gap) (97). Conversely, Currie (1993) (119) found that schizophrenics generated fewer reflexive, or express saccades, which is a finding that seemingly supports a disengagement deficit.

Of particular interest is the SC's involvement in the regulation of various stages of eye movement. Saccade and fixation cells of the SC together with cortical inputs from brain stem centers control fixation (120-122). Measurement within the SC reveal that saccade cells remain silent during attentive fixation, respond prior to and during a saccade, and are suppressed immediately after a saccade. Fixation cells respond during attentive fixation and remain silent during a saccade. The generation of a saccade requires activation of the saccade cells and inhibition of the fixation cells. The obverse is required to maintain fixation (121).

In order to further assess mechanisms of fixation and attention, schizophrenic saccadic eye movements were measured in the presence of distracter stimuli in the gap and overlap fixation conditions. Distracters were either onset prior to or after the onset of the target. Saccade latencies are increased if distracter stimuli are presented in close temporal proximity to the target (123, 124). This is termed *bilateral effect;* it occurs regardless of whether the subject is informed in advance of the target's position (125). In normals an auditory distracter selectively impaired visual target selection in the gap when compared to the overlap condition (126). The presence of a distracter significantly slows the latency to saccade for patients with schizophrenia as compared to normals (100). This effect is evident when the distracter appears following target onset (Figure 2). In addition, schizophrenics have a greater percentage of error saccades directed to the distracter as

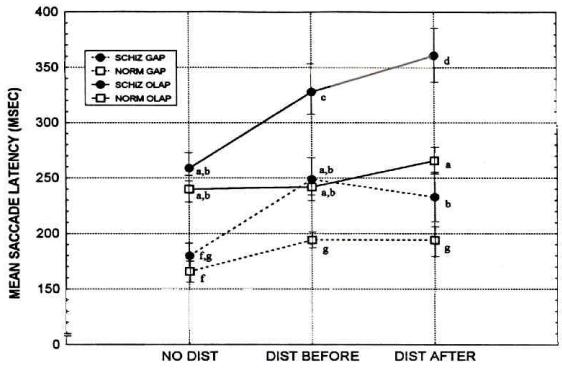

Figure 2. Mean saccade latency (± SEM) for normal controls and schizophrenics for the Group x Distracter x Fixation interaction. Conditions that do not share a common letter are significantly different ($p<.05$)

well as a longer latency to issue corrective saccades following an error saccade. The pattern of results in the presence of a distracter signifies that the process of orienting to the target by normals occurs in an automatic way (e.g., preattentive) while that of schizophrenics relies on volitional mechanisms. Although a disengage deficit mediated by cortical regions cannot be discounted a more probable explanation is that an imbalance exists in the mutual inhibitory pathways in subcortical/cortical regions (e.g., between saccade and fixation cells of the SC) in schizophrenia.

3.4.3. Smooth Pursuit Eye Movement (SPEM)

Smooth Pursuit Eye Movements (SPEM) is the process of visually following the path of a stimulus' steady movement. Smooth pursuit eye tracking is a measure of visual information processing ability and it is a complex task that requires the integration of several oculomotor and neurological functions. Current research proposes that SPEM consists of two stages: initiation and maintenance of pursuit. The first stage begins 100-150 ms after a target begins to move and is indexed by the initiation of target movement (127). Although this movement is initiated without significant cognitive involvement or regulation (128, 129), within the subsequent 125 ms, retinal image-sensory motion inputs begin to affect tracking with the objective of maintaining smooth pursuit (130). Once eye movement reaches a velocity similar to the speed of the target, smooth tracking begins and requires minor retinal adjustments to maintain the target on the fovea. These adjustments are modulated, in part, by attention. The most commonly studied indices of SPEM are square-wave jerks (SWJs), pursuit gain, and catch-up saccades (CUSs).

During pursuit, when the eyes lag behind the target a compensatory saccade is produced to "catch-up" to the target. Therefore, catch-up saccades (CUS) compensate for an inability to efficiently and accurately follow a target (i.e., low pursuit gain). Pursuit gain is 1.0 when target and fovea are superimposed temporally and spatially. When pursuit gain falls below 1.0 (i.e., the ratio of eye velocity to target velocity), CUS return the image of the target on the fovea (131). To this end, patients with schizophrenia are deficient in anticipating target position (131, 132) and they demonstrate a high prevalence of catch-up saccades.

Levin *et al* (1988) (133) used both predictable triangular wave and nonpredictable step ramp targets to study schizophrenic patients and normal control subjects. The results indicated that patients with schizophrenia were less adept than were normals in anticipating the turnaround point in the stimulus trajectory, as indicated by a significantly longer interval between direction reversal of eye and target movement. This interpretation is supported by Allen *et al* (1990) (134) and Kowler *et al* (1990) (135), who claim that anticipation is an integral part of pursuit behavior and that smooth pursuit participants construct an internal representation of target motion to anticipate the target's future location.. Furthermore, Thaker and colleagues (1996) (87), using step-ramp and single step tasks, reported significantly lower accuracies of CUSs in schizophrenic patients than in normal control participants, an observation that is further supported by Ross, Thaker and colleagues (1997)) (88). Sweeney and colleagues (1999) (90), examined the "diagnostic specificity and long-term effects of visual tracking deficits in schizophrenia using step-ramp tasks". The findings were consistent with other step-ramp studies that observed abnormalities in open- and closed-loop pursuit gain as well as diminished accuracies of CUSs (80, 81, 91 92, 133). Therefore, CUSs are among the important microcomponents in maintaining smooth pursuit in the overall SPEM system.

Since the first report on disordered smooth pursuit eye movements in schizophrenics by Diefendorf and Dodge (1908) (136) smooth pursuit abnormalities within this group continue to be well documented. Additional findings include observations of SPEM abnormalities occurring in first-degree relatives of schizophrenics (56, 73, 76, 84, 85, 137-150) with severe eye tracking deficits noted in schizophrenics with a positive family history of schizophrenia (81, 86, 89). To this end, an eye tracking dysfunction (ETD) (i.e., abnormal saccades and smooth pursuit) is proposed as a genetic marker / trait for vulnerability to schizophrenia (73, 142, 151).

To further qualify attention and information processing with respect to eye movement dysfunctions, Schwartz, *et al.* (1999) (93) evaluated if specific temporal epics are associated with the degree of decreased tracking accuracy of schizophrenics. To accomplished this a sinusoidal wave was divided into 12 temporal (i.e., velocity) "within wave" bins (i.e., "temporal windows"). Schizophrenics' eye tracking performance did deviate from normal controls on total time in smooth pursuit, percentage of time in smooth pursuit, and total saccade time. Notably the tracking deficit was restricted to temporal epochs of low and high target velocity. Thus, for patients with schizophrenia, the target velocities were unable to optimally activate motion detection cells (e.g., transient/magnocellular). In turn, deficits at higher velocities reflect a restricted temporal resolution for transients. In support of a transient/magnocellular deficit, Stuve *et al.* (1997) (152) observed a negative correlation

between schizophrenics' smooth pursuit gain and motion processing threshold that was independent of sustained attention. More recently Holzman (2000) (2) and Chen *et al* (1999ab) (91, 92) have observed a deficit of velocity sensitivity in schizophrenics that is correlated with the initial acceleration of smooth pursuit and peak gain. These results strongly support the "notion" that patients with schizophrenia exhibit a marked deficit in the motion processing system that is mediated by transient cells of the M pathway.

Of particular interest is the recent reports that saccadic eye movements and smooth pursuit eye movements (SPEM) are possibly mediated by the same neuroanatomic areas (153, 154). For example, the superior colliculus and the frontal eye field (FEF) are neuroanatomic loci involved in the regulation of saccades, fixation and SPEM. While not discounting the important contribution of the FEF, Sweeney and colleagues (1998), Chen and colleagues (1999a, 1999b), Thaker and colleagues (1996, 1998), and Ferrara and Lisbergerger (1995, 1997) (81, 87, 91, 92, 155, 156) have identified the middle temporal area (MT) which is involved in the analysis of visual motion and the medial superior temporal (MST) which combines visual information with eye movement as the focal area for processing visual motion inputs to the pursuit system and the saccade system. Lesions (either those that naturally occur in humans or those experimentally produced in monkeys) and microstimulation of these areas are known to disrupt motion information processing in the pursuit and saccade system as well as contributing to delayed saccade latency to a stationary target. The SPEM and saccadic eye movement systems are discrete yet interrelated which is evidenced by their anatomical interconnectedness. The implications for a dysfunction in a common regulatory mechanism involving SPEM, saccadic eye movement, and attention are manifold and the effects are amongst those herein reviewed. An additional area where information processing diverges from normals is sensory gating.

3.5. Sensory Gating

Schizophrenia is often conceptualized as arising from basic cognitive deficits (e.g., deficits in attention) according to Freedman, *et al.* (1999) (74). However, yet to be determined is the biological bases for cognitive deficits. Therefore, research is in progress to identify the biological marker that will assist in the search for a phenotypic definition of schizophrenia (62, 157). Investigators have previously relied on genetic-epidemiological (i.e., twin and adoption) studies (158). The implication from these studies is that schizophrenia likely results from the interaction of several genes instead of a single gene. The manner in which the gene(s) expresses itself is, in part, influenced by environmental factors. Thus individuals most likely inherit a predisposition towards the disease rather than the actual disease itself.

Linkage studies are a common approach to the study of a genetic vulnerability to schizophrenia. Linkage occurs when the close proximity of a genetic marker and a diseased gene results in family members of schizophrenics having the marker and disease more frequently than is expected by chance (102, 157). Research suggests that schizophrenia "clusters" in families, however it does not show Mendelian transmission like other diseases such as Huntington's disease or cystic fibrosis (70, 159, 160). It is suggested that targeting phenotypes – information processing deficits (e.g. backward masking, saccades and SPEMs) and sensory gating deficits- (e.g., pre-pulse inhibition utilizing the P50 event related potential (ERP)) provides significant utility over that of identifying the etiology of schizophrenia itself (158, 159). Evaluation of the P-50 auditory evoked potential has provided information pertinent to the identification of a phenotypic biological marker as well as providing another procedure that is used to assess attention and information processing.

Pre-pulse inhibition of the P50 auditory evoked potential is an electrophysiologic procedure that presents two discrete auditory stimuli. The cerebral electrophysiologic activity evoked by a stimulus is referred to as an event related potential (i.e., ERP). In normal controls the P50 response that occurs to a second auditory stimulus is suppressed (referred to as gating) owing to inhibition or gating by the first auditory stimuli. Sensory gating, therefore, is part of the information processing system that is involved in the initial screening of stimuli, selection of relevant stimuli and inhibition of irrelevant stimuli (161). In the schizophrenia spectrum disorders, including schizotypal disorder, schizophrenics fail to show a reduced response to the second pulse, referred to as an (P50) inhibitory deficit (75).

Inhibition of response during sensory gating is modulated by nicotinic cholinergic neurotransmission (70, 75, 162, 163). This finding is supported by animal models in which disruption of cholinergic neural transmission disrupts sensory gating (162). The cholinergic system participates in cognitive tasks to include an indirect association with learning and memory, with more direct involvement of attentional processes (164). Therefore, an increase in cholinergic receptor activation has the potential to enhance cognition or more specifically, attentional performance.

In addition to sensory gating, nicotinic receptors are implicated in the "pathogenesis" of several brain disorders such as Alzheimer's and Parkinson's disease, attention deficit / hyperactivity disorder, depression, and schizophrenia (165). Not only do these diseases and disorders have in common a memory, cognition and attention deficit, they also have a shared decrease (underactivity) / depletion of dopamine activity or dopamine release promoting action in the prefrontal cortex. According to Adler *et al* (1992), nicotinic administration (e.g., smoking, patches, gum) improves attentiveness. In fact, tobacco use is highest among schizophrenic patients compared to normal controls and this behavior is suggested to represent a form of self-medication; when tobacco use is ceased, schizophrenic symptoms worsen (165). The effects of nicotine, however, are likely related to dopamine (as well as other neurotransmitter) release. Thus we revisit the hypothesis that excess activity at certain dopamine synapses is associated with the schizophrenia spectrum disorders. Because dopamine modulates the efficiency of

visual information processing as well as that of transient function (19) (i.e., in that dopamine modulates rapid sequential information processing), a dysregulation in these components is likely to be pertinent to the dysregulation of information processing by schizophrenics. Thus, attention / information processing deficits of schizophrenics can index a disruption of the dopamine system and reflect a parallel dysfunction in the regulation of the magnocellular fiber' transient response to visual information.

The findings from the Freedman, *et al.* study (1999) on the P50 evoked response links the inhibitory deficit to the chromosome 15q14 locus of the alpha-7 nicotinic receptor. This likely implicates (a) candidate gene(s) for the neurobiological mechanism of schizophrenia as well as an alternative phenotype for linkage analyses (163). By isolating a discrete deficit it is possible to reflect the activity of a single gene (74). Based on this finding, the P50 deficit is increasingly becoming accepted as a phenotypic biological marker for neuronal dysfunction in schizophrenia.

4. CONCLUSION

Attention deficits are pervasive among schizophrenic patients however, they are not restricted to patients with schizophrenia. These deficits have been identified in first-degree relatives of schizophrenics as well as within the schizophrenia spectrum disorders (e.g., schizotypy). Thus, attention may serve as a variable "trait" marker for the schizophrenia spectrum disorders. Tasks that evaluate information processing converge to indicate a temporal processing deficit in schizophrenics that occurs at approximately 100 milliseconds. Of particular interest is that the deficit occurs during the time period closely associated with a dysfunctional inhibitory mechanism that is maximally activated during the 100 millisecond time period (e.g., during the period of temporal integration). The inhibitory mechanism is conceptualized by Schwartz *et al* (1982)as well as others as being a "transient" or "fast" system involved in the serial / sequential processing of information.

Within the visual pathways, transient-response type neurons of the M pathway respond preferentially to motion stimulus onset and offset and coarse objects, whereas sustained response-type neurons of the P pathway respond preferentially to slow moving or stationary stimuli and fine detail objects. In schizophrenics, visual information processing deficits are proposed to result from an inhibitory defect between transient and sustained activity of magnocellular or parvocellular neurons respectively (44, 50) such that activity within sustained-type neurons persists owing to decreased inhibition of activity by transient-type neurons. Amongst numerous models, the magnocellular / transient deficit appears to be the most applicable as an explanation for the majority of findings.

A temporal processing deficit is further supported by smooth pursuit eye movement (SPEM) findings of poorer performance on tracking extreme velocities by schizophrenics. Therefore, the implication is slower stimulus velocities do not appear to optimally activate transient cells. Among schizophrenics SPEM performance is enhanced in response to nicotine exposure (e.g., cigarette smoking) (166), a response that is similar to the response of the P50 event related potential (ERP) to nicotine. Studies of the P50 ERP have supported other findings that illustrate the inability of schizophrenic patients to select relevant stimuli and inhibit irrelevant stimuli.

Saccadic eye movement/attention tasks reveal that saccade and fixation neurons in the superior colliculus (SC) respond in an analogous manner to transient and sustained activity. The SC receives a significant afferent projection from transient retinal ganglion cells (15, 33), the visual, the frontal, and the parietal cortices while sending its efferents to the brainstem nuclei involved in the generation of saccadic eye movements (167, 168). Therefore it is inviting to speculate that deficits of visual processing and eye movement / attention deficits share a common mechanism. Deficits observed in backward masking studies and saccade deficits (in the presence of distracters) could also involve a common inhibitory mechanism. Specifically, an abnormal inhibitory relationship between transient and sustained activity in the former and between saccade and fixation cells in the latter.

The model of attention proposed by Vidyasagar (1999) (41) supports this position in that (he) addresses the effects of interchannel modulation. In this model, the faster conducting M-system processes information in parallel across the entire visual field. Subsequently, interchannel activity between the M and P pathways highlights or spotlights divisions of the P pathway that represent pertinent objects for further processing. Consequently, deficits of cognitive processes dependent upon parvocellular function are secondary to magnocellular dysfunction.

Schizophrenia, is a complex disease with many manifestations that include complex symptomotology with a marked deficit in attention / information processing. Various measures of this deficit include, but are not limited to, psychophysical tasks that strongly implicate a deficit within the neurophysiologic visual pathways. From the aforementioned studies it is clear that significant advances have been made in the understanding of the attention / information processing deficit. Future research will undoubtedly provide additional convergent findings to explain schizophrenic information processing and attention deficit.

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