Orienting Response Research in Schizophrenia: Where We Have Come and Where We Might Go

by Alvin S. Bernstein

Abstract

This review and critique of orienting response (OR) research in schizophrenia examines the initial Western work, outlines current positions, and notes several areas in which further lines of research are needed. Discussion involves characteristics of schizophrenic patients who are OR nonresponders; OR nonresponding as a possible trait marker; the question of OR nonresponding in child patients; the association between negative symptoms and OR nonresponding as well as the possible existence of a specific subgroup marked by emotional withdrawal and cognitive disorganization; slow habituation as a prognostic index in high-risk children and adult acute patients; the need for research into defensive and startle responses as well as the OR, and possible interactions among them; electroencephalographic-autonomic differences in OR; and the need to explore the functional meaning of OR nonresponding in schizophrenia.

It is now 20 years and more since persistent efforts began in the United States and Western Europe to study attentional processes in schizophrenia through the orienting response (OR) (e.g., Bernstein 1964; Zahn 1964; Maltzman and Raskin 1965; Dykman et al. 1968), and some sort of overview seems in order.

Initial Work

On the basis of work in the Soviet Union, the OR was initially thought to be associated with the very onset of attention, triggered by the detection of any stimulus “novelty” (Sokolov 1960, 1963). Luria (1973) thus called the OR “the most elementary form of attention.” A powerful correspondence between the OR and attentional processes has been sustained by Western research as well, leading Öhman (1979) to conclude that the OR “is central to the systems controlling what aspects of the flow of events will receive attention, central processing, and learning” (p. 466).

Recent Western study has identified the OR more specifically with the allocation of a limited capacity central processor (or with the call for such a processor), operating only after the activation of preattentional, automatic, parallel processing channels (Öhman 1979; Dawson et al. 1982; Siddle and Packer, in press). Despite its relatively late position in the information-processing sequence, OR-associated capacity allocation can occur quickly. Filion et al. (1986) reported a latency within 150 ms.

The attentional nature of the OR, and the consensus, going back to Kraepelin and Bleuler, that basic deficiencies of attention exist in schizophrenia suggested the OR as an area of study. In addition, the physiological nature of the system was itself attractive. (The OR involves identifiable responses in skin conductance, finger pulse volume, pupillary dilation, cardiac deceleration, alpha blockade, changes in skeletal muscle activity, including changes in respiration pattern [Sokolov 1963], as well as the $P_{300}$ component of the evoked potential [Ritter et al. 1968; Roth 1973; Nash and Peralme 1986].)

It appeared that by applying skin-surface electrodes, one might not only be able to obtain information

Reprint requests should be sent to Dr. A.S. Bernstein, Dept. of Psychiatry, Box 32, SUNY Health Sciences Center at Brooklyn, 450 Clarkson Ave., Brooklyn, NY 11203.
about a vital aspect of attention, but do so from a wider, more representative sample of the schizophrenic population as well, including those patients who were so unraveled and unmotivated as to be inaccessible to laboratory study by other means. If so, it might represent an important advance over the practice of working with relatively coherent, accessible patients, and generalizing from them to the entire schizophrenic population.

The importance of distinguishing within schizophrenia was soon made clear. Zahn et al. (1968) found greater loss of skin conductance response (SCR) OR in hebephrenic than in paranoid schizophrenic patients, a finding confirmed by Bernstein (1969). Bernstein (1964, 1969) reported that schizophrenic patients displaying cognitive disorganization (unfortunately labeled “confused”) showed more frequent SCR OR nonresponding to innocuous stimuli than did those who were more intact (“clear”), with the hebephrenic-paranoid distinction apparently part of this general pattern.

The 1960’s also produced a major conflict, typified on one side by my own work reporting deficient OR in schizophrenia, with many patients nonreactive and others showing abnormally rapid habituation, and by Zahn’s work on the other side, indicating that while heightened initial nonresponding occurred, schizophrenic patients were essentially overreactive, showing a failure to habituate OR or an unstable habituation.

Beginning in 1972, Gruzelier and Venables suggested a resolution in their “bimodality hypothesis.” Schizophrenia, they said, consisted in roughly equal measure of a subgroup that failed to respond to innocuous stimuli, and another essentially unable to stop responding. Zahn and I were thus said to be each half right (Venables 1975). Elaborating on their hypothesis (e.g., Gruzelier and Venables 1973, 1975; Gruzelier and Hammond 1977; Gruzelier et al. 1981b), they suggested a synthesis based on the identification of two subpopulations within schizophrenia, one showing OR nonresponding associated with amygdaloid dysfunction and the other showing OR nonhabituation associated with hippocampal dysfunction. Recording SCR from each hand led them to conclude further that the limbic dysfunction existed in the left hemisphere (Gruzelier 1973; Gruzelier and Venables 1974).  

1While a general review of the possibility of lateral OR asymmetry in schizophrenia is beyond the purpose of this article, some comment is in order. First raised by Gruzelier (1973) with SCR OR, this has been tested repeatedly. In an incomplete listing, Bernstein et al. (1985a) cited 10 such studies—each failure to replicate the original report. Bernstein et al. (1981, 1985a, 1986) extended the search to finger pulse volume (FPV), but found no such evidence here. Recently, Gruzelier (1984) reported a different SCR asymmetry in schizophrenia, with greater right- than left-hand SCR said to be associated with negative symptom features, greater left- than right-hand SCR with more florid symptoms. This has not yet received the testing in other laboratories needed to establish reliability. In general, however, one must be cautious in reading asymmetry of brain function from peripheral systems. For example, Toone et al. (1979) found no lesion-associated changes in SCR after unilateral hippocampal or amygdaloid ablation for epilepsy. EEG evidence seems more ambiguous, with some studies reporting it and some not (even in the same laboratory—Bernstein et al. 1985a). (See Merrn 1981; Seidman 1983) Even if such asymmetry is ultimately confirmed in schizophrenia, differences between EEG, autonomic, and  

Some writers (e.g., Zahn 1976; Bernstein et al. 1980) remained unconvinced that the bimodality hypothesis could reconcile the apparent conflict in the OR literature. For example, “bimodality” fails to explain how all amygdaloid nonresponder patients migrated to my laboratory, while all hippocampal overresponders ended up in Zahn’s. With each investigator drawing from large metropolitan areas, the odds against such chance outcomes are enormous. Further, as Venables and Bernstein (1983) noted, although a bimodal OR distribution was replicated in the Gruzelier-Venables laboratory, this was not true elsewhere with the sole exception of Rubens and Lapidus (1978). Some others have seen slow-habituating schizophrenic patients (Frith et al. 1979; Bartfai et al. 1983) but not as part of a bimodal distribution of schizophrenic OR.

I shall return later to the issue of slow habituation in schizophrenia. For now I wish to make it clear that slow-habituating schizophrenic patients are seen. They appear in my data too, especially when more intense stimuli are used (Bernstein 1970). However, most studies eliciting slow habituation from schizophrenic patients also reveal slow habituation from an equal or greater proportion in control samples. For example, while Cohen et al. (1981) reported 35 percent of their schizophrenic subjects failed to habituate to 15 75-decibel (dB) tones, 45 percent of their alcoholic subjects, and 64 percent of their normal controls also failed to do so. Similar data are presented by Bernstein, Struabe, Patterson, and Frith in Bernstein et
al. (1982). Thus, the incidence of slow-habituating ORs among schizophrenic patients is often unremarkable (Öhman 1981), or actually provides further evidence of hyporesponsiveness.

**Current Position**

A wider consensus has recently emerged about the nature of the OR in schizophrenia. One factor in this was a multinational study examining SCR OR in six laboratories in the United States, Britain, and Germany (Bernstein et al. 1982). One virtually unanimous finding emerged: on average, 40-50 percent of the schizophrenic populations were nonresponsive to innocuous stimuli of moderate intensity. This was true whether they were long-hospitalized chronic or first-hospitalization acute patients, on or off medication, and whether auditory or visual stimuli were used. Similar results were subsequently reported from Sweden (Alm et al. 1984). Additional factors in the new consensus were extensive reviews by Öhman (1981), Venables and Bernstein (1983), and Dawson and Nuechterlein (1984), each arriving at the same conclusion: the existence of a large group of schizophrenic nonresponders is “almost universally replicable” (Venables and Bernstein 1983, p. 477), while that of an abnormally large group of hyperresponders is not reliably demonstrated across laboratories.

Progress appears to have been made as well toward understanding why some have reported slow-habituating schizophrenic patients, with (Gruzelier and Venables 1972; Rubens and Lapidus 1978) or without bimodality (Frith et al. 1979; Bartfai et al. 1983). In the multinational study (Bernstein et al. 1982), only Frith and Gruzelier-Venables saw no evidence of rapid OR habituation in schizophrenic patients. Reanalyzing their data, Frith et al. (1982) found their evidence of slow habituation to have been artificial, due to excessive nonspecific cutaneous electrodermal fluctuations (NSF) in schizophrenic subjects (something observed by many investigators), compounded by the use of longer (1-5 sec) latency windows to define SCR OR rather than the 1-3 sec used (more appropriately; Levinson and Edelberg 1985) by those reporting fast habituation. Given greater NSF, longer response windows allowed more artificial “ORs” among schizophrenic subjects. On correcting for such artifact, Frith et al. (1982) concluded: “Our results are [now, with much previous work in showing an abnormally rapid rate of skin conductance habituation in schizophrenia” (p. 583). Levinson et al. (1984, 1985) and Levinson and Edelberg (1985) supported these findings.

With substantial agreement that we can identify a distinctive subgroup of schizophrenic OR nonresponders, work could turn in a direction urged by Buchsbaum and Haier (1983) among others. Attempts to study the heterogeneity of schizophrenia by defining symptomatically homogeneous subgroups and seeking their biological parameters have had limited success. Instead, Buchsbaum and Haier suggest exploring the parameters of subgroups defined on the basis of biological criteria. OR nonresponding might define such a group, and exploration of their parameters has begun.

First, some housekeeping work was needed. Since everything described so far was studied in the SCR OR component alone, it was possible that nonresponding might exist solely in this peripheral system and not in the central OR. It was necessary to record independent OR components simultaneously. In three studies (Bernstein et al. 1981, 1985a, 1986) we have now reported that SCR OR nonresponders with chronic schizophrenia generally are simultaneously nonresponsive in the finger pulse volume (FPV) OR as well. Straube has confirmed this in Germany with acute patients (personal communication, 1986). Since SCR and FPV are independent measures (Prout 1967; Bini et al. 1980), this points to OR absence in these patients rather than to peripheral deficit. Further confirmation comes from Steinhauer and Zubin (1982) and Friedman et al. (1973), who both reported that schizophrenic patients with impaired pupillary dilation OR also showed $P_{x0}$ deficit (though Cohen et al. [1981] reported $P_{x0}$ was impaired equally whether patients were SCR responders or nonresponders), while Patterson (1976) and Straube (1979a) both found reduced pupillary light reflex in schizophrenic subjects who were SCR OR nonresponders.

**Characteristics of Schizophrenic Subjects Who Are OR Nonresponders**

Working as suggested by Buchsbaum and Haier (1983), it was learned that nonresponder schizophrenic patients did display a distinctive symptom pattern. Using the Brief Psychiatric Rating Scale (BPRS), Straube (1979b) and Bernstein et al. (1981) found nonresponders to be characterized by high levels of emotional withdrawal and cognitive disorganization. Focusing on the emotional withdrawal ratings, both authors emphasized a relation between negative symptoms and OR nonresponding within
schizophrenia. This is broadly consistent with Gruzeler’s (1976) work with the Wittenborn Psychiatric Scale showing more florid symptoms among “noninstitutionalized” schizophrenic subjects who are OR responders, while more withdrawn patients among “institutionalized” OR responders showed smaller amplitude SCR ORs.

This relationship between reduced OR and social/emotional withdrawal does not appear to be a consequence of hospitalization, medication, or being labeled “schizophrenic.” Venables et al. (1978) identified a group of OR-nonresponsive 3-year-old children who on followup at age 6½ already displayed more social isolation and less constructive play than did OR responder children. Further support appears in work with college students identified by Chapman Scale scores (Chapman and Chapman 1985) as high in anhedonia (diminished capacity for pleasure, a quintessential “negative” feature), or in perceptual aberration (a “positive” feature reflecting perceptual distortion). Anhedonic students were hyporeactive in several OR components, while aberrant students were not (e.g., Simons 1981; Bernstein and Riedel, in press).

Other findings of interest in defining the characteristics of schizophrenic nonresponders include those of Schneider (1982) that among chronic schizophrenic patients (who generally display more negative features) those with the least OR show poor response to neuroleptics, while more floridly disturbed acute patients do not show this relationship (Zahn et al. 1981). Alm et al. (1984) noted a trend for schizophrenic nonresponders to display poorer premorbid adjustment, and a stronger finding that OR nonresponders often have blood relatives diagnosed schizophrenic, while responder patients commonly are the sole cases of schizophrenia among their blood kin.

**OR Nonresponding as a Possible Trait Marker for a Subtype of Schizophrenia**

Following Zubin and Spring (1977), one can ask whether OR nonresponding is a state/episode marker of schizophrenic illness or a relatively permanent trait/vulnerability marker of the schizophrenic individual. To establish the latter, nonresponding must be evident not only during a clinical episode, but before and after it as well. Studies of remitted schizophrenic patients by Iacono (1982) and Zahn et al. (1981) have shown that the incidence of OR nonresponding does not decline with clinical remission. Further, studies with the Chapman Scale noted above found increased nonresponding in anhedonic students apparently at risk for schizophrenia (and thus perhaps “preschizophrenic”) as well.

Citing this evidence, Dawson and Nuechterlein (1984) concluded that OR nonresponding is a promising vulnerability marker, but wondered “whether the vulnerability being indexed is genetically determined ... and whether [it] is specific to schizophrenia” (p. 225). Alm et al. (1984) have provided evidence of genetic determination. Whether OR nonresponding is specific to schizophrenia remains an important question; all the more so since recent reports have claimed a similar incidence of nonresponding among depressed patients (e.g., Janes and Strock 1982; Iacono et al. 1983, 1984), while Lutzenberger et al. (1983) claimed that anhedonics, in whom OR deficit has also been noted, might actually be predepressive rather than preschizophrenic. Thus, work with both depressives and anhedonics has recently suggested that OR nonresponding may occur in affective as well as schizophrenic disorders.

My own laboratory has begun to explore these areas. Our initial findings with depressives (Bernstein et al. 1986) suggest that a key factor here may lie in the same source of ambiguity that marked the early schizophrenia studies—namely a concentration on SCR alone. Bernstein et al. (1986) found, again, that schizophrenic patients were generally nonresponsive to innocuous tones in both SCR and FPV, normalizing in both when significant signals were presented. This is consistent with earlier findings showing many schizophrenic patients to be nonresponsive to innocuous stimuli in SCR, FPV, pupillary dilation, and P300 systems. The common thread tying these systems together is the fact that each is a component of the OR.

In contrast, Bernstein et al. (1986) found that while depressives were indeed often SCR nonresponsive to innocuous stimuli, they showed normal response in FPV. Given significant signals, they remained normally responsive in FPV but failed to normalize SCR. Bruno et al. (1983) also reported unimpaired FPV response in depressives, while Steinhauser and Zubin (1982) found normal pupillary dilation here, and the P300 data are uneven at best, some reporting no impairment (e.g., Friedman and Meares 1979; Giedke et al. 1981), while others see diminished P300 in depressives (e.g., Barbiere-Braun and Lesvre 1983). This evidence of normal FPV, pupillary dilation, and (often) P300 responses strongly suggests it is not the OR that is deficient in depression.

A consistently deficient response has been reported in depressives,
but in three specific systems—SCR, forearm blood flow response (FBF), and salivary output. Many have noted reduced SCR in depression, even to tones of 120-dB intensity (Greenfield et al. 1963). Diminished increase in FBF during mental arithmetic among depressives was noted by Kelly and Walter (1969) and Bruno et al. (1983), among others, while diminished salivary output has been reported by Noble and Lader (1971) and others. Thus, depressives, too, have been shown to be consistently deficient in a variety of responses. Here, however, what ties the deficit-prone systems together is not the OR but the fact that all are cholinergically mediated.

Where schizophrenic patients display deficient OR, depressive patients appear to display a specifically cholinergic dysfunction.

With regard to the anhedonia literature, initial research with Chapman’s physical anhedonia scale (Chapman and Chapman 1985; Simmons 1981, 1982) did suggest that a student subgroup at specific risk for schizophrenia was identified. However, Lutzenberger et al. (1983) showed that patients hospitalized with severe depression had anhedonia scores as high as those of schizophrenic patients, and concluded that high anhedonia may identify risk for depression as well as, or instead of, that for schizophrenia.

Bernstein and Riedel (in press) applied the response patterns reported by Bernstein et al. (1986) to differentiate schizophrenic from depressive samples to this issue, and found that anhedonic students gave schizophrenic-like rather than depressive-like patterns. This supports the Chapmans’ original contention linking high anhedonia specifically to risk for schizophrenia. Further support was provided by Miller and Yee (1985), who found that evoked potential data showed differences between dysthymic and anhedonic samples.

Bernstein and Riedel (in press) suggested two conclusions, both bearing on the issue of developing vulnerability markers for schizophrenia. One is that while students high in anhedonia may show heightened rates of schizophrenia as a group, it might be those combining anhedonia with OR hypofunction who are specifically vulnerable within this population. Second, the relationship of anhedonia to schizophrenia and depression may depend on a trait/state distinction. Research to date has shown that hospitalized patients with schizophrenia and depression both display heightened anhedonia, while college students showing high anhedonia without being diagnosable as schizophrenic or depressive do not show inflated (Beck) depression scale scores (Beckfield 1985), but do show psychophysiological patterns resembling those of schizophrenic patients. This network of results suggests that heightened anhedonia may be a state characteristic associated with both schizophrenia and depression, but that marked anhedonia in individuals not clinically diagnosable for psychosis may be a trait characteristic associated with that subgroup of schizophrenia centering on isolation and loss of motivation.

Thus, our depression and anhedonia data and those of Miller and Yee (1985), as well as the genetic data from Alm et al. (1984), suggest that OR nonresponding may indeed be schizophrenia-specific and genetic in origin—but replication and further study are sorely needed.

For the genetic determination of nonresponding, further work must test the persistence of OR nonresponding itself across blood relations and not just the persistence of schizophrenic diagnoses. For further tests of the specificity of OR nonresponsiveness to schizophrenia, the inclusion of pupillary reactions would be helpful, allowing specific adrenergic/dilation versus cholinergic/constriction activity to be tested within the same subject. For the present, the data support the reasonable (though still tentative) conclusion that OR nonresponding may be a vulnerability marker for what Alm et al. (1984) called “a core group of severely schizophrenic patients” (p. 205) who appear to be characterized by genetic transmission of schizophrenia, a poor premorbid picture marked by social-emotional isolation, and the gradual onset of a psychosis showing poor response to neuroleptics, negative symptoms, and cognitive disorganization. The apparent similarity between these features and those describing Crow’s (1980) Type II schizophrenia deserves investigation, although an initial effort by Alm et al. (1984) to compare ventricle-brain ratio (VBR) in schizophrenic responders and nonresponders found nonsignificant differences rather than the enlarged VBR said to characterize Type II patients.\(^2\)

\(^2\)Actually, it is difficult at present to predict a specific relationship between enlarged VBR and OR nonresponding. While Alm et al. (1984) showed a relationship between family history for schizophrenia and OR nonresponding, the literature for enlarged VBRs is unclear, with some reporting enlarged VBR to be associated with a negative family history (e.g., Murray et al. 1985) and others disputing this (e.g., DeLisi et al. 1985).
OR Nonresponding in Child Patients

Additional comments can be made about the diagnostic specificity of OR nonresponsiveness, but this time concerning what some may regard as a surprisingly narrow focus.

The literature dealing with child or adolescent psychoses has not reported heightened OR nonresponsiveness (e.g., Bernal and Miller 1970; Itil et al. 1974; Bernstein and Taylor 1976; White et al. 1976; see James and Barry 1980). The same is true of the work with children genetically at risk for schizophrenia (e.g., Mednick 1978; Erlenmeyer-Kimling et al. 1979; Prentky et al. 1981).

There is still dispute about whether early onset psychosis is related to adult schizophrenia (James and Barry 1980, p. 507). The OR literature thus may suggest that childhood and adult psychoses are discontinuous, with only the latter marked by OR deficit. If they are held to be a single pathology, one must account for the sudden onset of massive nonresponding in early adulthood. Available data are too weak to provide answers, partly because there are so few studies here, and partly because many of these use diagnostic criteria that are vague, outdated, and sometimes idiosyncratic (e.g., Bernal and Miller studied “autistic schizophrenics”). The issue remains of interest.

Recent, Weinberger (1986) suggested that schizophrenia may be the result of subtle, static brain lesions of early origin that do not make their appearance (as adult schizophrenia) until the brain areas involved reach physiological maturity, in late adolescence or early adulthood. Study of the OR seems to offer another means of examining the continuity of schizophrenia in children and adults.

Negative Symptoms and OR Nonresponding, or Is There a Specific Emotionally Withdrawn-Conceptually Disorganized Subgroup?

There now appears to be agreement that OR nonresponding in schizophrenia is associated with negative symptoms, and that these center on signs of withdrawal. For example, Zahn’s (1986) recent review concludes:

The data do suggest that, compared to global severity, a more relevant clinical dimension for OR frequency might be activity versus withdrawal, or positive versus negative symptoms. [p. 518]

To the extent such conclusions depend on evidence of emotional withdrawal on the BPRS (Straube 1979b; Bernstein et al. 1981), they may need further thought, and certainly need further research with better indices of negative symptoms.

In a factor-analytic study of the BPRS, Guy (1976) reported that emotional withdrawal loaded with motor retardation, blunted affect, and (slightly) disorientation on a factor called “Anergia.” The nature of these items suggests support for emotional withdrawal as a negative symptom. (Cognitive disorganization loaded together with grandiosity, hallucinatory behavior, and unusual thought content on an independent factor called “Thought Disturbance.”)

Unfortunately, other evidence suggests that emotional withdrawal by itself is an ambiguous index of negative symptomatology. Carpenter et al. (1985) consider that emotional withdrawal is often a secondary reaction to a primary positive symptom—i.e., two patients may receive identical withdrawal scores, due in one case to loss of interest, and in the other to a paranoid fear. Carpenter et al. emphasize the need for a narrower definition of negative symptoms focused on poverty of speech and flattened affect. The same point is made by Crow (1985) and Pogue-Geile and Harrow (1985), though the latter accept motor retardation as well. Angrist et al. (1980) provided evidence of the ambiguity of emotional withdrawal. Each of the presumed positive symptoms in the BPRS Thought Disturbance factor (Guy 1976) was increased by amphetamines and reduced by neuroleptics, as expected. Of the presumed negative Anergia symptoms, motor retardation and blunted affect were not affected by either drug, again as expected. However, emotional withdrawal showed the same response to each drug as did the positive symptoms.

This emphasis on negative symptom correlates of OR nonresponding, at least in the work of Straube (1979b) and Bernstein et al. (1981), depended not only on emphasizing the emotional withdrawal ratings, but also on ignoring the equally high conceptual disorganization ratings. Since such disorganization was shown to load on a separate positive-symptom factor (Guy 1976), ignoring it made interpretation easier (but not wiser). In my own case, it also meant ignoring earlier data showing the conceptually disorganized “Confused” patients to be the ones showing the greatest OR nonresponding (Bernstein 1969).

Furthermore, using a variety of rating scales, several other laboratories have also identified a subgroup of patients marked by both emotional withdrawal and conceptual disorganization, and noted them to be strikingly deficient across a wide range of functions. Using the Psychotic Reaction Profile, Fenz and Steffy (1968) reported electrodermal
nonresponsiveness among chronic female psychiatric patients was associated with cognitive disorganization and emotional withdrawal. Franzen and Ingvar (1975a, 1975b) found altered cerebral blood flow was most striking in patients displaying the greatest emotional withdrawal and cognitive disorganization, as rated by the Rockland-Pollin scale. Schooler and Goldberg (1972), relating ratings on the Inpatient Multidimensional Psychiatric Scale and the Ward Behavior Rating Scale to performance on tests of reaction time, word similarities, vocabulary, and ataxia concluded:

By far the greatest number of relationships are between performance and symptoms of withdrawal and cognitive disturbance. [p. 97]

Using multivariate techniques to define BPRS profiles in psychiatric patients, Overall and Hollister (1982) identified one of four “thinking disorder prototypes” as being high in emotional withdrawal, conceptual disorganization, and blunted affect, calling them a “Withdrawn-Disorganized” type.

The point to be made is not that negative symptoms are unimportant in OR nonresponding. Though any support for this based purely on BPRS emotional withdrawal ratings is shaky, there is additional support in the studies showing diminished OR in anhedonic, but not in perceptually aberrant students, and perhaps also in Venables’ report of social isolation in 6-year-old nonresponders. There is a need, however, to explore this area using more reliable indices based on poverty of speech, blunted affect, and perhaps motor retardation, rather than on emotional withdrawal alone.

It is also important at least to begin looking beyond purely negative or purely positive symptom correlates of schizophrenic dysfunction. 

The work cited above points to a “Withdrawn-Disorganized” subgroup, displaying both positive and negative features, and widely deficient across functions. More work must be done to determine whether this is, in fact, a clinically significant subgroup and to explore its parameters.

Slow SCR Habitation Among High-risk Children and Acute Schizophrenic Adults

Clearly, I do not wish to deny that negative symptoms may be an important factor in OR nonresponding in schizophrenia. In fact, an appreciation of the importance of negative symptoms appears to be vital to a proper understanding of two findings dealing ostensibly with SCR OR overreactivity in schizophrenia. For one, Mednick et al. (1978) reported that slow habituating electrodermal activity provided the best indicator of subsequent schizophrenia among high-risk children. While others have taken issue with specific items in the Mednick group’s data—for example, failing to confirm the rapid SCR half-recovery time emphasized by Mednick (Prentky et al. 1981; Zahn 1977)—there has been general, though not universal (e.g., Kugelmass et al. 1985), support for slow SCR habituation as a predictor here (e.g., Zahn 1977; Salzman and Klein 1978). In addition, Frith et al. (1979) and Zahn et al. (1981) reported that adults with acute schizophrenia who displayed slow-habituating SCRs were less likely to show rapid clinical remission.

Thus, overreactive ostensible ORs have been presented as an index of poor prognosis in both directions, marking those high-risk children most likely to slide into schizophrenia, and those adult patients least likely to slide out.

In understanding these findings, one must remember that Mednick et al. (1978) specified that their electrodermal index predicted only that type of schizophrenia associated with hallucinations and delusions; it was not predictive of future schizophrenia characterized by more negative or defect symptoms (Carpenter et al. 1985). Regarding fast SCR half-recovery, Mednick (1978) noted it “correlates rather well” (r = .49) with hallucinations and delusions. High-risk children who later developed schizophrenia without florid Schneiderian symptoms did not display fast SCR recovery.

Analogous statements can be made about the Frith and Zahn data. Both studied acute patients with marked Schneiderian symptoms, good prognoses, and little evidence of negative symptoms. Their electrodermal data may thus be reflecting differences between major schizophrenic subtypes. One showing an episodic, positive-symptom (schizophreniiform?) pathology may display slow electrodermal habituation as an index of poor short-term prognosis. The other, showing more strongly negative symptoms (together with cognitive disorganization?) and a generally poor prognosis, may be characterized more by OR deficit. Zahn et al. (1981) recognized this possibility, which was confirmed when Schneider (1982) showed that among chronic patients (who show more pronounced negative symptoms as a rule), it was those with the least OR who showed the poorest response to drug treatment.

It should also be noted that those reporting excessive SCR among high-risk children who later became schizophrenic obtained such results only to relatively unpleasant loud (96 dB) noise, never to innocuous tones (Mednick 1978; Salzman and
Klein 1978; Pretkyn et al. 1981). This raises the further possibility that what was observed was a proclivity to produce not ORs, but defensive responses (DRs).

**Defensive and Startle Responses**

Research in the past 20 years makes clear the brain’s capacity to modulate its information intake. In this context, the OR facilitates the intake of information from significant, and thus high priority (Bernstein 1979, 1981), stimuli. In addition, sustained stimuli that are unpleasant or unwanted elicit DRs, associated with skeletal muscle fight-or-flight preparation and with attenuation of stimulus intake (Sokolov 1963; Graham 1979, 1984). Graham and her associates have also shown that startle, sensitive to the rapid rise of transient stimulus intensity to critical levels within a few milliseconds, represents an “interrupt” system effectively clearing the board so that stimulus intake and muscle activity may be speedily redirected as dictated by the nature of the following stimulation.

Thus, the point worth exploring on the basis of the data from high-risk children and those from Zahn and Frith is that both the future development of florid schizophrenic pathology, and the decreased likelihood of early remission when such florid episodes appear, may not be signaled by slow habituating OR and excessive stimulus intake. Rather, it may be a predilection for premature DR (or startle), to stimuli considered innocuous by others, and an attentional system biased in a “gating out” posture psychologically (in terms of criteria) or physiologically (in terms of mechanism sensitivity) that prognosticates.

One failing of the research so far has been the neglect of the DR and startle responses. A full understanding of attentional functioning requires one to look at both facilitative and constraining mechanisms, since it is their interplay that helps determine information intake. Beyond this, the literature already provides intriguing suggestions that schizophrenia may be characterized by diminished intake-facilitative activity but undiminished—or even hyperactive—attenuating activity. In a rare study examining both systems, Dimitriev et al. (1968) did, in fact, report ORs to be widely hypofunctional in schizophrenia while DRs remained intact until the “terminal” stage.

In work that may bear on this distinction, both my laboratory and that of Gruzelier have shown nonresponsiveness in schizophrenia to be reduced if stimulus intensity is increased (Bernstein 1964, 1970; Bernstein et al. 1981; Gruzelier et al. 1981a, 1981b). Both research groups considered this a belated OR, triggered by more significant or “salient” stimuli. However, Öhman (1981) noted that the switch to responding occurred at about 90 dB, a level at which normal DR and startle begin to appear. Thus, the onset of responding here may not signal belated ORs but rather the onset of DRs. Lidsky et al. (1979) suggested precisely such a finding—i.e., that schizophrenic patients might display both absent ORs to mild stimuli and active DRs to slightly more intense stimuli, leaving only a constricted range within which they could function effectively.

However, this interpretation of the Bernstein and Gruzelier intensity-related findings is made unlikely by recent work showing normal SCR and FPV response when schizophrenic patients are given significance-targeted stimuli at the same intensity as the innocuous stimuli that produced frequent nonresponding (Bernstein et al. 1985a, 1986; Öhman et al., in press). The fact that the same normalized response appears whether one increases stimulus intensity or retains the moderate intensity but heightens signal significance suggests that the belated responses reported by Bernstein and Gruzelier are, in fact, ORs.

Other data seem to suggest that it may be the ostensibly “OR-responsive” subgroup that actually displays heightened DRs, mistaken for ORs. For example, Thayer and Silber (1971) found that schizophrenic responders described themselves as “anxious” or “startled” by the tones to which they responded. Gamborg (1965) found that of 42 schizophrenic patients given mild OR stimuli, 23 (55 percent) were nonresponsive. Of the 19 responders, 15 (79 percent) actually gave DRs—a far greater proportion than among controls. (A test on his data yielded \( \chi^2 = 18.8, p < .001 \).)

Studies of SCR or FPV can only give inferential evidence on the OR-DR issue since these do not qualitatively distinguish OR from DR. Other measures, including cardiac acceleration (e.g., Graham 1979; Orlebeke and Feij 1979) and increased blood flow to the forearm muscles (e.g., Abrahams et al. 1960; Rosenberg 1970), provide better indices of the DR. The few studies available here also yield interesting data. Zahn et al. (1968) found that of 42 schizophrenic subjects who were SCR-responsive to 72-dB tones displayed tachycardia at the same time—an “environmental rejection” response as Venables (1973) pointed out. Gruzelier and Hammond (1978) found that schizophrenic patients who were SCR-responsive to 75- or 85-dB tones showed not only accel-
iteratory heart rate (HR) responses, but higher systolic blood pressure and serum cortisol levels as well. (Higher background stress levels are associated with increased likelihood of displaying DR to a given stimulus [Waters and Wright 1979].) Kelly and Walter (1968) also found faster HR levels, plus higher forearm blood flow in schizophrenic patients, calling it evidence of "more persistent arousal of the defense reaction."

Such results suggest the possibility that many schizophrenic patients may find external stimuli unpleasant or fearsome before most other people do, and consequently react with DRs to stimuli eliciting ORs from others. Just this is concluded by Levine and Whitney (1970), who found that schizophrenic patients perceived a tone as "unpleasant" at lower intensity (70 dB on average) than did normal control subjects (81 dB). Dykman et al. (1968) noted that, unlike normal control subjects, 38 percent of their schizophrenic subjects found a tone of 60 dB "painful."

Two possible OR-DR interactions have thus been noted so far. One states that the OR nonresponder subgroup may be persistently OR-deficient but display DRs to intense stimuli that can be mistaken for SCR or FPV ORs. Studies with high significance-moderate intensity signals cast doubt on this interpretation. The other states that patients apparently responsive to innocuous stimuli may also be OR deficient, but display DRs at abnormally low stimulus intensities that are mistaken for SCR/FPV ORs. Further study is needed before any firm conclusion is possible here.

Yet a third possible interaction can also be noted. Most investigators have concluded that SCR (or FPV) amplitude reflects either OR or DR indistinguishably. (SCR half-recovery time may differentiate them, but this is in dispute [see Fowles 1986].) However, an opposing view, suggesting that DRs may be actively antagonistic to SCR OR, has also been presented. Horwitz and Kaufman (1979) noted that distension of the carotid sinus reduced skin potential activity, suggesting that DRs may inhibit electrodermal OR. (The relationship between cardiac acceleration and DR is believed to be mediated via distensive effects on carotid sinus and aortic arch baroreceptors.) In support, Simons et al. (1983) found SCR nonresponding to be associated with acceleratory, and SCR responding with deceleratory HR response, concluding that SCR nonresponding "may indicate a lower threshold for defensive responding" (p. 504). Similarly, Dykman et al. (1968) found that schizophrenic subjects with minimal SCR displayed HR acceleration (called a "stimulus rejection" pattern), while those with large SCRs gave HR deceleration (an "open" pattern). This raises still other questions about SCR nonresponders—i.e., do such patients simply not allocate ORs, or have they switched in DRs instead, inhibiting (SCR) ORs?

There are thus different strands of evidence suggesting, with varying degrees of support, several OR-DR interactions in schizophrenia. None of these issues have been explored. The only efforts I am aware of come from the U.S.S.R. (Gamburg 1965; Dimitriev et al. 1968), and bear the flaws of Soviet reports of that time—vague and incomplete description, lack of statistical testing, and unfamiliar diagnostic criteria. It is time to begin systematic study here.

There has been little work on startle in schizophrenic subjects, though long ago Strauss (1929) and Landis and Hunt (1939) found above-normal startle in schizophrenic subjects. More recently, Geyer and Braff (1982) noted that startle-blink latencies were faster, and habituation slower in schizophrenic subjects. Karson (1979) reported increased blink among schizophrenic subjects to glabellar tap (though Stevens [1978] found this not to be true of other schizophrenic subjects). Braff et al. (1978) showed a reduced diminution of startle blink following a weak lead stimulus in schizophrenic patients. Though due to an information-processing deficit, this reduced diminution leaves them more vulnerable to the distracting, interruptive effects of blink.

While reflex and endogenous blinks can be differentiated by latency and waveform (Stern et al. 1984), they appear to share intake-interrupt functions. Thus, Volkman et al. (1982) and Riggs et al. (1981) showed a suppression of visual function also with endogenous eyeblink. Wibbenmeyer et al. (1983) showed it was not due to muscle response since suppression occurred 35 ms preceding the blink. A similar effect was reported by Kennard and Glaser (1964), who concluded that blink may "interrupt all sensory functions of the brain" (p. 46).

It is thus of added interest that schizophrenic patients show higher rates of endogenous, as well as startle, blink (Stevens 1978; Cegalis and Sweeney 1979; Karson et al. 1981). This is not simply the result of neuroleptics or tardive dyskinesia (Stevens 1978) since Kraepelin described "increased winking" long before the drug era.

The literature thus indicates not only that schizophrenia is marked by a decrease in the activity of intake-facilitating ORs, but hints it may also be marked by excessive activity in a range of intake-limiting systems, including both DR and
startle/blink. Very little has been done to examine this, and OR-DR-startle interactions in schizophrenia are wholly unexplored. Research here is sorely needed, and must not be restricted to SCR and FPV. Multi-channel recordings, also involving blink and cardiovascular responses, that are better able to differentiate OR, DR, and startle are needed. Cardiovascular DRs are now known to have long latencies (at least 10–15 sec) and durations up to 60 sec (Graham 1979; Turpin and Siddle 1983), and this will have to be considered in new studies.

**EEG-Autonomic Nervous System (ANS) Differences**

My own multichannel studies have shown a lack of concordance between autonomic and EEG response in schizophrenia. On the basis of power spectral analyses, our background EEG data confirmed the findings of others—reduced alpha power, slowed dominant alpha frequency, and increased beta power (Shagass 1976; Bernstein et al. 1981, 1985a). In phasic response, however, we have found no impairment in the 4–29 Hz bandwidth studied, despite the deficit in autonomic response. Since our work shows that phasic EEG response in this band primarily involves the alpha band, our studies point essentially to a discrepancy between autonomic and EEG-alpha reactivity in schizophrenia.

It would be important to map any such CNS-ANS dissociations. However, disagreement with our findings is evident in at least one study. Dimitriev et al. (1968) reported EEG deficits among schizophrenic patients resembled those seen in their autonomic data, though details of method, scoring, and the like are too vague for close analysis. However, similar dissociation, involving absent electrodermal and cardiovascular OR together with unimpaired alpha block, has been reported elsewhere. Workers at Stanford repeatedly noted this following amygdalectomy in monkeys (Bagshaw and Benzies 1968; Bagshaw et al. 1972), despite the fact that such monkeys retain peripheral response capability (Bagshaw and Pribram 1968). In addition, work with aged human subjects has shown the same EEG-ANS dissociation (Marsh and Thompson 1977).

The implications of these reports are tantalizing (all the more so since Marsh and Thompson [1977] noted that "highly meaningful material" improved autonomic response in the aged, something seen as well in the schizophrenia literature to be noted below). Before studies exploring these implications can be undertaken, cross-laboratory evidence of the reliability of the phenomenon must be in hand (especially given the apparent contradiction between our findings and those of Dimitriev et al. [1968]).

At present one can only speculate. If this dissociation is a fact, and if the earlier literature (Sokolov 1960, 1963) is correct in categorizing alpha block as an OR component, it would suggest that while central and autonomic OR may be integrated in normals, they appear to disintegrate in many schizophrenic patients. Since the CNS OR appears, in this view, to be operating properly, it would be the withdrawal of convergent autonomic OR that might be contributing to the clinical picture.

Another possibility can also be considered. This sees alpha block not as an OR but as an index of preattentional stimulus detection processes, possibly associated with oculomotor changes. The Stanford group cited above have suggested that the alpha block is associated with stimulus detection, and not with the full processing and assimilation associated with autonomic ORs. Ohman (1979) accepted a similar distinction. Mulholland (e.g., 1973) considers alpha blockade to be associated with efferent adjustments of the oculomotor system (involving accommodation and vergence) rather than with the processing of afferent input, per se.

Such a view, i.e., considering alpha block part of a preattentional, pre-OR process rather than as an OR component, could also make sense of an apparent discrepancy between alpha block and P300 responses in schizophrenia. I noted earlier that several writers consider P300 to be an OR component and that the literature consistently reports a P300 deficit in schizophrenia. If alpha block is an OR, one must then explain why one EEG component seems to operate without impairment, dissociated from ANS components, while another shows a deficit consistent with that seen in autonomic responses.

Thus, the alternate speculation is that schizophrenic subjects may have intact preattentional stimulus detection capability (including preattentional oculomotor reactions), showing intact alpha block and rapid eye movement to peripheral stimuli (Cegalis et al. 1977), but deficient limited-capacity, full-scale processing, therefore showing deficient OR in both autonomic and P300 indices.

While P300 and autonomic OR are alike in revealing deficient responses in schizophrenia, there is also divergence between them which must be considered. P300 deficit appears in studies with significant stimuli, precisely where Gruzelier and we found autonomic OR to normalize in schizophrenic subjects (this will be
More normal-like initial allocation of attentional resources, consistent with autonomic OR. We were not then aware that Verleger and Cohen (1978) had already done this and confirmed our guess. “At least at the beginning of the individual trials,” they found, “schizophrenics and normals did not differ in their P300 reactions,” though schizophrenics subsequently showed P300 habituation and normals did not (p. 92). Thus, P300 and autonomic OR findings in schizophrenia may be concordant, after all, with each differing from the results seen in alpha block.

What Is the Meaning of Nonresponding In Schizophrenia?

To grasp the meaning of nonresponding, researchers first made use of the traditional conception of OR as an automatic product of any detection of stimulus uncertainty, and accordingly suggested schizophrenic nonresponders were unable to detect what happened around them (Maltzman and Raskin 1965; Bernstein 1969). Debate later developed about whether an OR was elicited by detection of uncertainty alone, or in interaction with an evaluation of stimulus significance (e.g., Bernstein 1979, 1981; O’Gorman 1979; Maltzman and Siddle 1979). My associates and I presented a series of studies concluding that the OR is triggered by uncertainty in a potentially significant stimulus, where the level of uncertainty detected determines whether central processing is needed, while stimulus significance determines whether allocation of limited channel space is justified (Bernstein et al. 1975; Bernstein and Taylor 1979; Bernstein et al. 1985a).

This raises the possibility that schizophrenic nonresponding might reflect idiosyncracy in the evaluation of stimulus significance rather than a loss of OR capacity or an inability to detect external stimuli. To test this, studies were conducted in my laboratory and Gruzelier’s, with similar results in both (Gruzelier and Venables 1973; Bernstein et al. 1980, 1981, 1985a, 1986; Gruzelier et al. 1981a, 1981b). These results suggest that OR nonresponse in schizophrenia may reflect an allocational decision, with schizophrenic deficit lying at the point in the attentional process where stimuli are weighed for significance and the decision is made whether to engage central attentional mechanisms, rather than in loss of detection, filtering, or OR capability, per se.

Despite the similarity between results in Bernstein’s and Gruzelier’s laboratories, the role of stimulus significance in OR responding in schizophrenia remains controversial. In particular, Zahn (e.g., 1986) reports increased differences from normals when schizophrenic subjects are given “meaningful” signals. Even here, however, some convergence has occurred. Zahn et al. (1981) reported that patients who showed prompt remission from an acute schizophrenic episode did show increased OR to significant tones (against a background of frequent nonresponsiveness to innocuous stimuli); only those who failed to remit within 3 months showed nonresponsiveness to both innocuous and significant signals. Recently, Öhman et al. (in press; their figure 1) reported that schizophrenic subjects with relatively fast reaction times (RTs) showed initially normal OR frequency to significant stimuli, while those with slow RTs remained OR nonresponsive here too. Thus, it may be important to study within-schizophrenic differences in the OR “normalization”
produced by significant stimuli since this may be associated with short-term prognosis and other factors of interest.

There is one other sense in which the meaning of OR nonresponding in schizophrenia remains obscure. A considerable literature links the OR with improved stimulus intake and assimilation in normals. It is surprising, then, that so few studies have tried to explore the effects of OR nonresponding on stimulus intake and assimilation in schizophrenia, and that these, on the whole, point to no coherent conclusions.

Straube (1979b) found that OR nonresponders displayed deficient auditory intake, while those who were OR responders did not; Gruzelier and Venables (1974) found nonresponder patients showed poor perceptual resolution in tests of twoflash threshold; Houlihan (1975) reported that schizophrenic subjects who displayed HR deceleration (an OR) to pretest stimuli showed better word recognition on tachistoscopic test trials than did patients who were HR accelerators.

While such findings are intuitively satisfying, given our understanding of the OR, others are less so. Straube was unable to replicate his finding (personal communication, 1985); Gruzelier and Hammond (1978) also reported responders to be poorer than nonresponders in tone discrimination; Patterson and Venables (1980) found poorer perceptual sensitivity in both nonresponders and normally habituating responder patients than in normals or rapidly habituating schizophrenic subjects; Alm et al. (1984) found no differences between responders and nonresponders in short-term memory. Roth et al. (1980) and Steinhauer and Zubin (1982) reported that schizophrenic subjects continued to display diminished $P_{\infty}$ (and diminished pupillary dilation in the latter study) even on trials where RT or stimulus-counting performances were matched to those of normal subjects. Bernstein et al. (1985a) and Ohman et al. (in press) reported that while schizophrenic subjects displayed a sharp drop in OR incidence to imperative RT signals after 20 or so presentations, their RTs did not mirror this drop, remaining parallel to the RTs of normal controls over trial blocks instead.

Thus, although we can now be reasonably sure that many schizophrenic patients display a marked absence of ORs to stimuli eliciting responses from other people, we cannot yet be sure what effects this has on the patient’s overall attentional performance. Stimulus discrimination, reaction time, and the like are related to stimulus-intake functions. Yet performance does not appear to undergo the decline one might expect in patients showing a decline in OR. The available data do not permit any coherent overall conclusions as yet.

Bernstein et al. (1985a) speculated about a reason for their dissociation of OR- and RT-attentional indices. They used a task that required subjects to press a foot pedal on alternating trials but did not inform subjects of this beforehand. Posttest interview revealed that control subjects soon became aware of the regular press/nonpress alternating nature of the task (as did those schizophrenic subjects with whom such interviews could be carried out). Thus, each could predict whether the next trial would be “press” or “ignore.” Temporal uncertainty remained, however, since no one could predict time of stimulus onset. Controls indicated concern for both response accuracy (which became easy with awareness of alternation) and with keeping RT speed within the 500-ms time limit set (which was not easy with the foot pedal used). Thus, controls may have remained OR attentive, not to identify stimulus type but to detect stimulus onset as early as possible.

Schizophrenic patients gave the impression of being less concerned with RT speed than with correctness. Once able to predict trial type, they may have disengaged ORs, relying instead on non-OR, preattentional processes to maintain RT levels. In short, the task may have been too simple to require OR, especially in someone relatively unconcerned about response speed.

Whether such speculation accounts for the Bernstein et al. (1985a) and Ohman et al. (in press) data cannot now be established. It does, however, help to make a final point: We need more work to answer the question, “What does it cost the schizophrenic nonresponder to be nonresponsive?” This work will have to be done with tasks that make strong demands on information processing rather than the essentially trivial demands that characterize much of the existing OR work.

OR studies of schizophrenia have produced interesting findings, and these increasingly are pointing to issues of clinical significance. Inevitably, as new data are gathered, they raise new issues and suggest new avenues of study. It is to some of these that I have tried to point.

References

Alm, T.; Lindström, L.; Öst, L.-G.; and Öhman, A. Electrodermal non-
responding in schizophrenia: Relationships to attentional, clinical, biochemical, computed tomo-


Bernstein, A., and Riedel, J. Psychophysiological response patterns in college students with high physical anhedonia scores appear to reflect schizotypy rather than depression. Biological Psychiatry, in press.

Bernstein, A.; Riedel, J.; Graae, F.; Seidman, D.; Steele, H.; Connolly, J.; and Lubowsky, J. “Schizophrenia Is Associated With Altered OR: Depression With Electrodermal (Cholinergic?) Deficit and Normal OR.” Presented at the Annual Meeting of the Society for Psychophysiological Research, Montreal, Canada, October 1986.


Bernstein, A.; Taylor, K.; Weinstein, E.; and Riedel, J. The effect of stimulus significance on relatively sustained (tonic like) and relatively


Fridt, C.; Stevens, M.; Johnstone, E.; and Crow, T. Skin conductance


Öhman, A. Electrodermal activity and vulnerability to schizophrenia:


Schneider, S. Multiple measures of hemispheric dysfunction in schizophrenia and depression.


Verleger, R., and Cohen, R. Effects of certainty, modality shift, and guess outcome on evoked potentials and reaction times in chronic schizophrenics. Psychological Medicine, 8:81-93, 1978.


Acknowledgment

Preparation of this article was supported in part by NIMH Grant #28594 to A.S. Bernstein.

The Author

Alvin S. Bernstein, Ph.D., is Associate Professor of Psychiatry, Department of Psychiatry, State University of New York Health Sciences Center at Brooklyn, Brooklyn, NY.

Schizophrenia: Questions and Answers

What is schizophrenia? What causes it? How is it treated? How can other people help? What is the outlook? These are the questions addressed in a booklet prepared by the Schizophrenia Research Branch of the National Institute of Mental Health.

Directed to readers who may have little or no professional training in schizophrenia-related disciplines, the booklet provides answers and explanations for many commonly asked questions of the complex issues about schizophrenia. It also conveys something of the sense of unreality, fears, and loneliness that a schizophrenic individual often experiences.

The booklet describes “The World of the Schizophrenic Patient” through the use of analogy. It briefly describes what is known about causes—the influence of genetics, environment, and biochemistry. It also discusses common treatment techniques. The booklet closes with a discussion of the prospects for understanding schizophrenia in the coming decade and the outlook for individuals who are now victims of this severe and often chronic mental disorder.

Single copies of Schizophrenia: Questions and Answers (DHHS Publication No. ADM 86–1457) are available from the Public Inquiries Branch, National Institute of Mental Health, Room 15C–05, 5600 Fishers Lane, Rockville, MD 20857.