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Journal Title: Archives of General Psychiatry
Volume: Volume 51, Number 7
Publisher: American Medical Association (AMA) | 1994-01-01, Pages 552-558
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1001/archpsyc.1994.03950070044009
Permanent URL: https://pid.emory.edu/ark:/25593/tqpjj

Final published version: http://dx.doi.org/10.1001/archpsyc.1994.03950070044009

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Accessed September 9, 2019 2:58 AM EDT
Impaired Autonomic Nervous System Habituation in Those at Genetic Risk for Schizophrenia

J. Meggin Hollister, MA; Sarnoff A. Mednick, PhD, DrMed; Patricia Brennan, PhD; Tyrone D. Cannon, PhD

**Background:** Schizophrenia has been associated with habituation of skin conductance activity. Skin conductance data from the Copenhagen High Risk Project were analyzed. We hypothesized that genetic risk for schizophrenia and development of schizophrenia later in life are related to impaired habituation of autonomic nervous system activity.

**Methods:** Data were collected in 1962, when subjects averaged 15 years of age and had not yet qualified for a psychiatric diagnosis. Nonspecific fluctuations in electrodermal activity were monitored during a rest period free of sensory stimulation.

**Results:** We found that an increasing level of genetic risk for schizophrenia was related to impaired habituation of autonomic nervous system activity over time. Individuals with two schizophrenia-spectrum parents evidenced no habituation, those with one spectrum parent evidenced some habituation, and those with normal parents evidenced rapid habituation. Subjects who developed schizophrenia in adulthood evidenced significant deficits in habituation in adolescence.

**Conclusions:** These results suggest that impaired habituation of spontaneous autonomic nervous system activity may represent a behavioral marker of the genetic predisposition to schizophrenia.

(Arch Gen Psychiatry. 1994;51:552-558)

Wen schizophrenia describe how they experience their disability, they emphasize the difficulty they have in tuning out (habituating to) incidental, nontarget stimuli that nonschizophrenics can successfully ignore. This failure of habituation may contribute to the attentional disturbances of schizophrenia. In research settings, schizophrenics evidence impaired habituation in startle reflex1-3 and skin conductance4-8 paradigms. Autonomic conditioning studies of children with schizophrenic parents have also reported habituation deficits.9,10 Twin studies have demonstrated that autonomic habituation (in humans) is strongly influenced by genetic factors.11,12 It is possible that the habituation deficit is a part of the genetically transmitted predisposition to schizophrenia.

The precise determinants of impaired autonomic nervous system habituation have not been established. Neuroanatomic substrates implicated in studies of skin conductance orienting are the prefrontal,13 pons, left temporal/amygdala regions,14-17 and the hippocampus.13-17 Other alternative mechanisms by which habituation may be affected include psychological factors, such as expressed emotion.

Using data collected as part of the Copenhagen High Risk Project, we examined habituation of autonomic nervous system activity in adolescents at three levels of genetic predisposition to schizophrenia: super high risk (SHR; both parents with schizophrenia-spectrum diagnoses), high risk (HR; one parent with a schizophrenia-spectrum diagnosis), and low risk (LR; neither parent with a schizophrenia-spectrum diagnosis). Electroder-
SUBJECTS AND METHODS

SUBJECT SELECTION

Risk Group Classification

Mednick and Schulzinger initiated the Copenhagen High Risk Project in 1962 to identify antecedents of schizophrenia. Subjects were classified by their genetic risk for schizophrenia. The study included 207 subjects in the HR group (offspring of schizophrenic mothers) and 104 subjects in the LR group (no history of hospitalization for mental illness in parents or grandparents) who were matched for sex, age, social class, and years of education (Table 1). An HR mother was required to have a diagnosis of schizophrenia according to the International Classification of Diseases, Eighth Revision, and 5 years of psychiatric hospitalization or at least three separate hospitalizations of 3 months or more, or an extended hospitalization plus a State Invalid Pension for Schizophrenia. Jorgensen et al. reexamined the HR mothers according to DSM-III criteria in 1987. They obtained hospital journals from all psychiatric admissions of the mothers up to 1975. Consequently, the rediagnoses included considerably more information than was available in 1962. After the rediagnosis, 92% of the HR mothers fulfilled DSM-III-R criteria for schizophrenia. In the Jorgensen article [published before DSM-III-R], 10 women were diagnosed as having atypical psychosis [DSM-III]. They met the criteria for schizophrenia except for their age at onset. By DSM-III-R criteria, these women were diagnosed as schizophrenic. The remaining 8% of mothers had the following diagnoses: schizophreniaiform, three; schizoaffective, two; schizoaffective followed by major depression, one; paranoid, three; and obsessive-compulsive disorder followed by personality disorder, not otherwise specified, one. The original 1962 diagnoses were conservative; almost all mothers later met DSM-III-R diagnostic criteria. The children of the entire group of mothers diagnosed as schizophrenic in 1962 were retained for analyses to maintain comparability with previous reports on this sample.

A diagnostic study of the HR subjects' biologic fathers was conducted in 1980 through 1983. Paternity was established by one or both of the following: the mother identified the father as the marital partner at time of conception, or the man was named on the child's birth certificate. Paternity was not verified through blood tests. Psychiatric hospital records were obtained on all fathers. Further more, all living fathers were asked to accept a home interview by a psychiatrist, which consisted of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version, characterologic items from the Current and Past Psychopathology Scales, and the Schizophrenic Spectrum Schedule (developed by Ronald O. Riener, MD). The maternal diagnosis was based on the interview and available case records according to Research Diagnostic Criteria (DSM-III criteria). If a father had a diagnosis in the schizophrenia spectrum (ie, schizophrenia, schizotypal personality disorder, or paranoid personality disorder), the children were assigned to the SHR group. Of the 207 HR subjects, 30 were found to have fathers with spectrum-disorder diagnoses, and 175 subjects were found to have fathers without spectrum-disorder diagnoses (two HR subjects were missing paternal psychiatric information). Therefore, the SHR group and the HR group consisted of 30 and 175 subjects, respectively. As indicated above, there were 104 subjects in the LR group.

Outcome Classification

Subjects were classified in one of three outcome groups: schizophrenia (SZ), other mental illness (OMI), and no mental illness (NMI). Recently, more than 90% of the original sample of SHR, HR, and LR subjects were reexamined by a psychiatrist. The interviewer was unaware of the results of the previous psychiatric assessments and administered the Schedule for Affective Disorders and Schizophrenia–Lifetime Version, the Present State Examination, the Present State Examination lifetime ratings of psychotic symptoms, the Present State Examination Syndrome Checklist for current and lifetime psychopathology, the Scales for the Assessment of Positive and Negative Symptoms, and the Personality Disorder Examination. Diagnoses of the subjects were established according to DSM-III-R criteria.

A total of eight SHR, 23 HR, and two LR subjects received lifetime diagnoses of schizophrenia. The SZ group was composed of the eight SHR subjects and the 23 HR subjects with lifetime diagnoses of schizophrenia. The two LR subjects who developed schizophrenia were not included in the analyses because they were not included in our "genetic risk" category. All subjects, regardless of risk group, who received a primary Axis I diagnosis of unipolar depression, bipolar depression, delusion disorder, schizophreniform disorder, atypical psychosis, alcohol abuse, drug-controlled stimuli were presented. Under such conditions, spontaneous fluctuations in skin conductance, or nonspecific responses (NSRs), are usually observed.

The rate of NSRs has been shown to decline over time in normal subjects. This pattern of response can be interpreted as autonomic habituation to one's surrounding static environment or to one's internal stimuli. In this study, habituation of subjects was measured by a de-
abuse, and organic brain syndrome were combined into the OMI group. The NMI group was composed of all subjects, regardless of risk group, with no sign of psychopathology as assessed by the interviewing psychiatrist.

INSTRUMENTATION AND PROCEDURES

Electrodermal response measures were taken in 1962 when the children were at a mean age of 15.1 years (range, 10 to 19 years) in a 50-minute morning session that consisted of a rest period followed by an experimental period. The psychophysiology laboratory was located in a light- and sound-attenuated room in the Kommunehospitalet, Copenhagen, Denmark. After washing and alcohol swabbing at points of electrode placement, the subject was asked to relax in a reclining position on a hospital bed. Two zinc Beckman cup electrodes, 7 mm in diameter (with sponges soaked in a zinc sulfate solution), were attached to the left hand of each subject to record electrodermal activity by means of a polygraph.

Electrodermal recording commenced 5 to 10 minutes after electrode placement and was performed continuously until the conclusion of the session. The first 90 seconds of the rest period were used to establish calibration. Therefore, data collection for the rest period commenced after a 6.5- to 11.5-minute hydration period. The subject was permitted to relax for 13.5 minutes (rest period) before experimental procedures began. The examiner remained still and out of sight of the subject. He noted any movement on the part of the subject and any noises that occurred in the laboratory. At the conclusion of the rest period, earphones were attached and the subject listened to instructions informing him or her of the procedure to follow. After a 70-second silent period after the instructions, eight presentations of a 1000-Hz, 54-dB tone occurred at intervals from 17 to 77 seconds to provide information about the subject's electrodermal orienting response. Any responses that occurred immediately after noises in the laboratory or movement on the part of the subject were noted by the examiner and not scored.

SCORING PROCEDURE

The rest period was divided into three blocks of 270 seconds each. An NSR was defined as a drop of 2.0% or more from the preceding resistance level. The mean number of NSRs for each block was computed. The NSR frequency was calculated as the sum of the NSRs across the three blocks for each subject. After a training period, interrater reliability was investigated by having two independent individuals score 20 records selected at random. The intraclass correlation for the three blocks for the two scorers was computed. The correlations for blocks 1, 2, and 3 were .97, .94, and .97, respectively. The intercorrelation of the total NSR scores for the two scorers was $r(19) = .99$.

We also examined habituation during the orienting trials that followed the rest period. The subjects listened to eight 1000-Hz, 54-dB tones through headphones, and the speed of habituation was measured by the number of tones presented to a subject before he or she had three consecutive nonresponses to the orienting stimuli.

STATISTICAL PROCEDURES

Rest Period

One-way analyses of variance (ANOVAs) were conducted with the total frequency of NSRs and the number of NSRs per block used as the dependent variables, and with the risk group classification (SHR, HR, and LR) as the independent variable. Additional one-way ANOVAs were conducted with the total frequency of NSRs and the number of NSRs per block used as the dependent variables and the diagnostic group (SZ, OMI, and NMI) as the independent variable. Newman-Keuls tests were conducted to examine further the differences between the groups.

Repeated-measure ANOVAs (RM-ANOVAs) were subsequently conducted for each group to assess the effect of block number on nonspecific responding. The average number of NSRs per block was analyzed in these analyses. Huynh-Feldt ε correction was used in the RM-ANOVAs to obtain adjusted $df$ when the Mauchly sphericity test was significant. The Mauchly test of sphericity examines the hypothesis that the variance-covariance matrix of the transformed variables (block number) used to test the effect (time) has covariances of zero and equal variances.

Orienting Trials

A correlation between the orienting habituation score and the third block score (the most sensitive indicant of habituation) was also computed. One-way ANOVAs were conducted with the orienting habituation score used as the dependent variable and genetic and diagnostic classification as the independent variables.

RESULTS

GENETIC RISK AND HABITUATION

The three risk groups differed in nonspecific responding (Figure 1). We calculated the total number of NSRs (blocks 1+2+3) during the entire rest period for the SHR,
HR, and LR groups; the means and SDs for the SHR, HR, and LR groups were 13.68±13.28, 10.82±11.17, and 8.22±8.30 (mean±SD), respectively. The differences in
NSR frequency were significant (F[2,299]=3.74, P=.02).
Newman-Keuls tests disclosed significant differences be-
tween the LR and SHR groups (P=.05) Note that the dif-
fferences in total NSR frequency mainly reflect differences that occurred in the second and third blocks.
An overall RM-ANOVA was used to probe the con-
tribution of the block variable to the group NSR dif-
fferences. Although the group×block interaction did not at-
tain conventional α levels required for statistical
significance (F[3,32,457]=.92), generally such omni-
bus tests of interactions lack statistical power,32 and for
this reason it has been recommended that focused con-
trasts be used to assess specific scientific hypotheses of
interest.32,33
An RM-ANOVA that combined all subjects into a
single sample demonstrated a significant effect of block
(F[1.65,457]=.98, P=.0004) that reflected habituation.
However, when the sample was divided into the three risk
groups and tested separately, a significant effect of block
was not observed for the SHR group (F[2,56]=0.09), which
reflected a lack of habituation. A significant effect of block
was observed for the HR group (F[1.64,257]=5.00, P=.01),
which reflected some habituation. A significant effect of
block was observed for the LR group (F[1.41,127]=5.83,
P=.009), which indicated habituation. Further evidence
of habituation differences was demonstrated by paired t
tests, which showed significant differences in the LR group
between blocks 1 and 2 (t[92]=2.02, P=.013) and be-
tween blocks 1 and 3 (t[90]=2.52, P=.012).
Significant differences were also revealed in the HR group between blocks 1 and 2 (t[159]=8.68, P=.001) and between blocks 1 and 3 (t[157]=5.84, P=.001). Thus, the LR and HR groups evi-
denced habituation. Nonsignificant differences between
blocks were observed for the SHR group, indicating a lack
of habituation.
An alternative series of analyses was also infor-
mative in understanding the group differences in NSRs as a
function of block. The three groups did not differ in mean
number of NSRs during the first block of the rest period
(F[2,280]=0.667, P=.51). Group differences almost
reached significance for block 2 (F[2,296]=2.52, P=.08).
A significant difference was observed among the three
risk groups in block 3 (F[2,294]=5.93, P=.003).
The means and SDs corresponding to these group
and block variables are shown in Table 2. By the third
block, the HR group evidenced rapid habituation, the HR
group evidenced an intermediate level of habituation, and
the SHR group evidenced little or no habituation (Table 2,
Figure 1). Newman-Keuls tests disclosed significant dif-
fferences in block 3 between the LR and HR groups and
between the LR and SHR groups (P=.05).

**DIAGNOSTIC CLASSIFICATION
AND HABITUATION**

The SZ, OMI, and NMI groups did not differ in overall non-
specific responding (F[2,280]=1.74, P=.18). The means

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Table 1. Sociodemographic Characteristics of the Super High-Risk, High-Risk, and Low-Risk Groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Super</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>30</td>
<td>175</td>
<td>104</td>
</tr>
<tr>
<td>Boys</td>
<td>15</td>
<td>101</td>
<td>59</td>
</tr>
<tr>
<td>Girls</td>
<td>15</td>
<td>74</td>
<td>45</td>
</tr>
<tr>
<td>Mean age in 1962</td>
<td>15.3</td>
<td>15.0</td>
<td>15.1</td>
</tr>
<tr>
<td>Mean social class†</td>
<td>2.5</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Mean years of education</td>
<td>7.2</td>
<td>6.8</td>
<td>7.3</td>
</tr>
</tbody>
</table>

*Age expressed in years.
†On a scale of 0 (low) to 6 (high).

Table 2. Nonspecific Responses in Blocks 1, 2, and 3 by Genetic Risk Groups and Diagnostic Groups

<table>
<thead>
<tr>
<th>Risk group</th>
<th>No. of Nonspecific Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>n²</td>
</tr>
<tr>
<td>Low</td>
<td>3.63±4.71</td>
</tr>
<tr>
<td>High</td>
<td>4.17±4.96</td>
</tr>
<tr>
<td>Super</td>
<td>4.67±5.59</td>
</tr>
<tr>
<td>Diagnostic group</td>
<td></td>
</tr>
<tr>
<td>No mental illness</td>
<td>4.15±4.87</td>
</tr>
<tr>
<td>Other mental illness</td>
<td>3.59±3.98</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>4.66±5.83</td>
</tr>
</tbody>
</table>

*Numbers of subjects differ because of missing data. Only subjects with complete data across the three blocks were included in the repeated-measures analyses of variance. All subjects were included in other analyses.
and SDs for the SZ, OMI, and NMI groups were 13.44±16.26, 10.83±10.92, and 9.61±9.44, respectively.

By RM-ANOVA, a nonsignificant group×block interaction was observed (F[3,35,352]=1.93, P=.12). However, a significant group×block interaction (F[1.65,297]=3.22, P=.01) and a significant main effect of block (F[1.65,297]=3.44, P=.04) were observed in a two-group RM-ANOVA that compared the SZ and NMI groups. The NMI group habituated during the rest period whereas the SZ group did not (Figure 2).

By RM-ANOVA, a nonsignificant effect of block was observed for the SZ group (F[2,56]=1.65). A nonsignificant effect of block was observed for the OMI group (F[2,156]=0.30). A significant effect of block was observed for the NMI group (F[1.58,242]=10.89, P=.0001), which reflected the general tendency of these subjects to habituate during the rest period.

The three groups (SZ, OMI, and NMI) did not differ in mean number of NSRs during the first block of the rest period (F[2,262]=0.638, P=.53). Group differences were not significant for block 2 (F[2,277]=0.87, P=.42). A significant difference was observed among the three groups in block 3 (F[2,277]=4.31, P=.01). Table 2 gives the means, SDs, and numbers of subjects. Newman-Keuls tests disclosed significant differences between the SZ and NMI groups (P=.05). Differences were not significant between the SZ and OMI groups, nor between the OMI and NMI groups. In Figure 2, the SZ group shows the least habituation, the OMI group shows a similar pattern, and the NMI group evidences habituation.

**ORIENTING HABITUATION**

The correlation between the orienting habituation score and the third block NSR score was r=.49, P<.05. Given the reliability of the two measures, this correlation indicates that the two measures are tapping similar habituation response tendencies. The mean (±SD) orienting scores for the risk groups, although not significantly different, were in the expected direction: SHR, 2.42±1.89; HR, 2.15±2.07; and LR, 2.0±1.77. The mean orienting scores for the diagnosis groups were not significantly different: SZ, 2.43±2.31; OMI, 2.03±2.05; and NMI, 2.23±1.88. Although the difference was not significant, the SZ group demonstrated poorer habituation than did the NMI group.

**COMMENT**

Our findings confirm the hypothesis that an increased level of genetic risk for schizophrenia is related to impaired ability to habituate autonomically to a relatively static environment. Poor habituation may be a part of the constellation of heritable factors that contribute to the cause of some types of schizophrenia.

Subjects in our sample who became schizophrenic in adulthood also evidenced significant deficits in habituation in adolescence; their rate of NSRs was higher at the end of a rest period than at the beginning. The large variance among the schizophrenics may reflect the genetic etiologic heterogeneity of the clinical condition of schizophrenia. A future study examining the symptoms and their relationship to habituation in childhood is planned. Children who developed schizophrenia in adulthood demonstrated significantly different patterns of habituation than children who were classified "not mentally ill" in adulthood. The habituation differences between those who became schizophrenic and those who developed other mental illnesses were not as striking. However, the habituation deficits in the SZ group were greater than those observed in the OMI group. Our findings suggest that habituation abnormalities in childhood may not be specific to those subjects who develop schizophrenia later in life.
OTHER FACTORS RELATING
SCHIZOPHRENIA AND HABITUATION

The neuroanatomic substrates controlling the process of habituation are not established. However, the hippocampus has been shown to be important in the regulation of behavioral and autonomic habituation. Abnormality of the hippocampus is one of the most consistently replicated findings in neuropsychology studies of schizophrenia. The hippocampus develops rapidly during the second trimester. The hippocampal anomalies observed in neuropsychology studies of schizophrenics and the impairment of habituation may be a consequence of the genetically triggered second-trimester disruptions in neural development, hypothesized by Mednick et al.

Psychological factors may also influence electrodermal activity habituation. Persistent and vivid thoughts and images may be more characteristic of the adolescent who will later be schizophrenic. Such thoughts may produce NSRs. Differential reaction to stress may affect electrodermal activity. Tarrier et al. examined differences in electrodermal activity between schizophrenics from families with high and low expressed emotion. They reported that both patient groups showed higher than normal rates of NSRs and were indistinguishable when only the experimenter was present. However, after a relative entered the room, the subjects from the low-expressed-emotion families showed a gradual decline in response frequency (habituation), whereas those from families with high expressed emotion continued to exhibit elevated response frequency (failed habituation). These results suggest that being in a high-expressed-emotion family may be a source of impaired habituation in the schizophrenic relatives.

In addition to habituation deficits, attention and information processing abnormalities have been noted in patients with schizophrenia. These deficits in attention and information processing may be related to habituation abnormalities. Habituation is critical for efficient information processing. If an individual is unable to reduce responsiveness to repeated stimulation (i.e., habituation), he or she may become overwhelmed by stimulation and become cognitively fragmented. If the failure to habituate produces an inability to cease attending to irrelevant external or internal stimuli, then we should find that individuals with increased NSRs will evidence attentional deficits. In a study that used a selective attention task, Ohman et al. reported an increased number of both NSRs and attentional deficits in a group of schizophrenics. Perhaps poor habituation impaired the ability of their patient group to attend selectively to target stimuli or filter out nontarget stimuli. In a 1981 study, Zahn et al. suggested that slow habituation of the orienting response, increased nonspecific responding, and slower reaction time are related to fluctuations in attention for schizophrenic subjects.

SUGGESTION FOR FUTURE RESEARCH

Typically, total NSR frequency is considered a measure of arousal. If we had noted only total NSR frequency, we might have concluded that the SHR and HR groups were simply more aroused. By examining responsiveness over time, we were able to conclude that the groups differed not only in number of responses but also in their pattern of responding. This finding should be considered in future studies that use NSRs as a dependent variable. A 15-minute examination period will probably show a different pattern of NSR production than a 5-minute period will. Such differences in the length of the period of measurement may explain why NSR findings in schizophrenia are sometimes conflicting.

Accepted for publication February 25, 1994.

This research was supported by National Institute of Mental Health grants MH41469 and MH46014 and by National Institute of Mental Health Research Scientist Award MH00619 (Dr Mednick).

Special thanks are extended to Michael Dawson, PhD, and Adrian Raine, PhD, for their helpful suggestions.

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