Original Investigation

Developmental Trajectories of Impaired Community Functioning in Schizophrenia

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IMPORTANCE Community functioning is a core component of the functional deficits in schizophrenia, yet little systematic research on the origins of these functional deficits has been performed.

OBJECTIVES To examine 3 key domains of community functioning—social activity, independent behavior, and functioning in school or work—before first hospitalization for schizophrenia and to determine whether these domains are familial.

DESIGN, SETTING, AND PARTICIPANTS In this population-based, prospective study that included a sibling-control comparison, data from the Israeli National Draft Board Registry were linked with data from the Israeli Psychiatric Hospitalization Case Registry. The merged file included data for all male adolescents who visited the draft board and were followed up for as much as 25.4 years from draft board assessment (through the end of 2010). The 3 functional domains for cases, their unaffected siblings, and controls were compared by time between assessment and time to hospitalization. Analyses were conducted from March 13, 2014, to October 19, 2014.

MAIN OUTCOMES AND MEASURES The trajectories and familiality of 3 key components of community functioning—social activity, independent behavior, and functioning in school or work—in the years preceding hospitalization for schizophrenia.

RESULTS Participants included 723 316 Israeli male adolescents who underwent a mandatory behavioral assessment to determine eligibility for military service. Linkage identified 3929 individuals hospitalized for schizophrenia. Data for 338 550 sibling pairs, 1659 hospitalized with schizophrenia, were similarly ascertained. Among those with schizophrenia, impairments in social activity (effect size $d$, 0.55) and functioning in school or work ($d = 0.37$) were recognizable up to 15 years before hospitalization. Independent behavior seemed preserved until the few years before first admission. For social activity, differences between cases and controls were progressively greater for patients admitted closer to time of testing ($F = 115.33$, $P < .001$). Unaffected siblings had small impairments compared with controls in social activity ($F = 28.25$, $P < .001$) and functioning in school or work scales ($F = 14.77$, $P < .001$). Group familial (sibling) correlations were relatively high for social activity ($r = 0.40$; 95% CI, 0.39-0.41) and functioning in school or work ($r = 0.50$; 95% CI, 0.49-0.51) but nil for independent behavior ($r = 0$; 95% CI, −0.01 to −0.01). Impairments in siblings had no progressive increase and were unrelated to their affected sibling’s time of illness onset (time trend: social activity: $F = 5.463$, $P = .02$; independent behavior: $F = 0.908$, $P = .34$; and functioning in school or work: $F = 1.386$, $P = .24$).

CONCLUSIONS AND RELEVANCE Various components of impaired community functioning in schizophrenia followed different developmental trajectories. Our results indicate that impairments in social activity and functioning in school or work are familial.
Impaired Community Functioning Trajectories in Schizophrenia

Methods

Assessment of Community Functioning

Most Israeli male adolescents (aged 16-17 years) undergo a cognitive, behavioral, and psychiatric draft board assessment to determine eligibility for military service. Part of this assessment entails a structured interview administered by college-aged individuals who complete a 4-month training on the administration of draft board tests.

This interview evaluates, among other things, 3 domains of community functioning (Table 1). Reliability and validity of the interview measures have been extensively tested by the draft board, and population-based norms are available for each test.26,27 The social engagement and functioning in school or work domains are highly correlated with equivalent domains of the Premorbid Adjustment Scale.28

National Psychiatric Hospitalization Case Registry

The Israeli National Psychiatric Hospitalization Case Registry includes a complete listing of all psychiatric hospitalizations in the country. The record of each hospitalization includes International Statistical Classification of Diseases, 10th Revision (ICD-10), diagnosis codes assigned at discharge. All inpatient psychiatric facilities in the country, including day hospitals and psychiatric units in general hospitals, are required by law to report to the register. Reporting is monitored by a special unit of the Ministry of Health that verifies reporting adherence and consistency of information, thereby ensuring completeness and correctness of the registry.29 In this study, we identified all patients with a final discharge diagnosis of schizophrenia (ICD-10 codes F20.0-F20.9).

Registry Linkage

After receiving approval from the Israeli Defence Forces Medical Corps Institutional Review Board and the local institutional review board, functioning data were linked with records of the hospitalization case registry by using the national identification number (equivalent to the US Social Security number) as the linking variable. For individuals who visited the draft board and who appeared in the hospitalization registry, final discharge diagnoses were added to the file. The national identification number was then removed to preserve pa-
tient confidentiality. A small proportion of individuals included in this analysis were also used in an earlier report. However, in addition to addressing different questions, the cohort in the present study also includes unaffected siblings, is substantially larger, and has a longer follow-up period. Analyses were conducted from March 13, 2014, to October 19, 2014.

Sibling Pairs
To examine familiality of premorbid impairment in community functioning, we created a file in which patients hospitalized for schizophrenia were matched with their unaffected siblings. These sibling pairs were compared with sibling pairs in which both were unaffected (comparison group). Siblings that were assessed more than 10 years apart from the patient and twin pairs were excluded. Because of possible intrafamilial correlation, only one affected patient and one nonaffected sibling (closest in age) per family were included in the analyses.

Statistical Analysis
First, interdependence among the 3 functional domains (ie, how well impairments in one domain predicted deficits in the other) was examined with linear regression analyses. To examine which of the 3 community functions were already impaired before illness onset, differences in functional impairments between the general population and future schizophrenia cases were estimated with univariate analyses of covariance. The potential confounders of immigration, socioeconomic status, and IQ were entered as covariates. To limit this analysis to adolescents with no obvious signs of disease during draft board assessment or with impairments in community functioning due to lower IQ, we dichotomized: those with very poor or poor functioning (scores, 1-2) were compared with those with adequate, good, or superior functioning (scores, 3-5). Siblings with functional impairments and patients who were also impaired were considered concordant pairs. Siblings who were not functionally impaired and patients with schizophrenia who had functional impairments were defined as nonconcordant pairs. The RR was calculated as follows: (Concordant Pairs/Concordant Pairs + Nonconcordant Pairs)/Percentage Socially Impaired in the Comparison Group. We used the χ² test to test for significance of the RR values by comparing the percentage of functionally impaired in the sibling group with the percentage of functionally impaired in the control group.

Finally, intraclass correlation coefficients (ICCs) were used to quantify the extent to which severe impairments in community functioning co-occurred in sibling pairs. To estimate whether this correlation was higher in affected families than unaffected families, we repeated the same procedure in unaffected sibling pairs. Because of the large sample size, P < .001 was considered statistically significant in all analyses.

Results
Cohort Characteristics
The merged file included data of all male adolescents who visited the draft board (n = 935,040) and were followed up for as much as 25.4 years from draft board assessment (through the end of 2010) (mean, 9.9 years; range, 0-25.4 years). Of these, 723,316 had functioning data, an IQ greater than 70, and a valid family identifier and were not hospitalized for a psychotic disorder other than schizophrenia for at least 365 days after visiting the draft board. Of these, 3929 were eventually hospitalized for schizophrenia. The sibling-pair analyses included 338,550 individuals, with 1659 sibling pairs with one affected and one unaffected sibling and 167,616 comparison sibling pairs.

Interdependence of Functional Impairments
We examined the interdependence of the 3 functional domains. The proportion of shared variance was significant but...
small (independent behavior [dependent variable] and social activity [independent variable]): $\beta = .327$, $R = 0.305$, $R^2 = 0.093$, $P < .001$; functioning in school or work [dependent variable] and social activity [independent variable]: $\beta = .105$, $R = 0.117$, $R^2 = 0.014$, $P < .001$; and independent behavior [dependent variable] and functioning in school or work [independent variable]: $\beta = −.005$, $R = 0.006$, $R^2 = 0.000$, $P < .001$).

**Developmental Trajectories**

Figure 1 shows that patients with schizophrenia had premorbid impairments only in 2 components of community functioning: social activity (standardized mean difference effect size $[d] = 0.55$) and functioning in school or work ($d = 0.37$). Differences between cases and controls in social activity increased as time between hospitalization and time of testing decreased (time trend: $F_{1,3559} = 115.33$, $P < .001$). Figure 2 shows that social activity impairments first increased approximately 15 years before first hospitalization, further increased 5 years before hospitalization, and continued to increase thereafter. Impairment in independent behavior started increasing 5 years before hospitalization (time trend: $F_{1,3559} = 20.38$, $P < .001$). No statistically significant overall change in the magnitude of impairment in functioning in school or work was evident ($F_{1,3559} = 1.813$, $P = .17$), but Figure 2 suggests a trend toward a decrease in functioning approximately 8 years before hospitalization.

**Between-Group Comparisons for Familiality**

Figure 2 shows that unaffected siblings had small impairments compared with controls in social activity ($F_{1,227,593} = 28.25$, $P < .001$) and functioning in school or work ($F_{1,227,593} = 14.77$, $P < .001$). Group familial (sibling) correlations were relatively high for social activity ($r_g = 0.40$; 95% CI, 0.39-0.41) and functioning in school or work ($r_g = 0.50$; 95% CI, 0.49-0.51) but nil for independent behavior ($r_g = 0$; 95% CI, −0.01 to −0.01).

In contrast to patients, impairments in siblings had no progressive increase (Figure 2) and were unrelated to their affected sibling’s time of illness onset (time trend: social activity: $F_{1,2395} = 5.463$, $P = .02$; independent behavior: $F_{1,2395} = 0.908$, $P = .34$; and functioning in school or work: $F_{1,2395} = 1.386$, $P = .24$).

**Within-Family Comparisons for Familiality**

Demographic and functional data of the matched sibling pairs used for within-family comparisons are presented in Table 2. Patients had significantly fewer years of education...
**Table 2. Sociodemographic Characteristics of Patients With Schizophrenia, Their Siblings, and Controls**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients vs Controls</th>
<th>Siblings vs Controls</th>
<th>Mean (SD) for Controls</th>
<th>Siblings vs Controls</th>
<th>P Value</th>
<th>Mean (SD) for Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational level, y (&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>11.05 (1.30)</td>
<td>11.32 (1.10)</td>
<td>11.05 (1.38)</td>
<td>11.32 (1.10)</td>
<td>&lt;.001</td>
<td>11.32 (1.16)</td>
<td>.97</td>
</tr>
<tr>
<td>IQ (&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>94.14 (13.14)</td>
<td>97.09 (13.79)</td>
<td>94.14 (13.00)</td>
<td>97.09 (13.79)</td>
<td>&lt;.001</td>
<td>100.56 (13.76)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SES (&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>11.16 (4.00)</td>
<td>11.08 (3.96)</td>
<td>11.16 (4.00)</td>
<td>11.08 (3.96)</td>
<td>&lt;.001</td>
<td>11.55 (4.18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of admissions</td>
<td>4.41 (5.18)</td>
<td>4.41 (5.18)</td>
<td>4.41 (5.18)</td>
<td>4.41 (5.18)</td>
<td>.15</td>
<td>4.41 (5.18)</td>
<td>.15</td>
</tr>
<tr>
<td>Total No. of days in the hospital</td>
<td>302.25 (490.36)</td>
<td>302.25 (490.36)</td>
<td>302.25 (490.36)</td>
<td>302.25 (490.36)</td>
<td>1.00</td>
<td>302.25 (490.36)</td>
<td>1.00</td>
</tr>
<tr>
<td>Immigrant status (yes/no), No. (%)</td>
<td>170 (10.2)</td>
<td>166 (10.0)</td>
<td>170 (10.2)</td>
<td>166 (10.0)</td>
<td>&lt;.99</td>
<td>42562 (10.2)</td>
<td>&lt;.99</td>
</tr>
<tr>
<td>Social activity score</td>
<td>2.71 (0.79)</td>
<td>2.92 (0.75)</td>
<td>2.71 (0.79)</td>
<td>2.92 (0.75)</td>
<td>&lt;.001</td>
<td>3.06 (0.72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Independent behavior score</td>
<td>3.06 (0.77)</td>
<td>3.14 (0.74)</td>
<td>3.06 (0.77)</td>
<td>3.14 (0.74)</td>
<td>.04</td>
<td>3.14 (0.66)</td>
<td>.04</td>
</tr>
<tr>
<td>Functioning in school or work score</td>
<td>2.71 (0.90)</td>
<td>2.86 (0.85)</td>
<td>2.71 (0.90)</td>
<td>2.86 (0.85)</td>
<td>&lt;.001</td>
<td>3.01 (0.81)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: d, effect size; SES, socioeconomic status. Ellipses indicate data not applicable.  
<sup>b</sup> Values are given for educational level, IQ, SES, age at first admission, number of admissions, and total number of days in the hospital; Ï‡ values are given for the 3 community functioning domains.  
<sup>c</sup> The IQ estimate is based on the sum of scores of the Otis-R, Similarities-R, Wechsler Adult Intelligence Scale (assessing verbal abstraction and categorization), Arithmetic-R, and Raven’s Progressive Matrices-R.  
<sup>d</sup> The SES is based on number of persons per room in the home, number of computers per household, number of motor vehicles per household, per capita income, and educational level.  
<sup>e</sup> The SES is based on number of persons per room in the home, number of computers per household, number of motor vehicles per household, per capita income, and educational level.

**Table 3. Relative Risk Estimates and Number (Percentage) of Impaired Patients, Siblings, and Controls**

<table>
<thead>
<tr>
<th>Impairmenta</th>
<th>Patients With Impaired Community Functioning, No. (%)</th>
<th>Siblings of Patients With Impaired Community Functioning, No. (%)</th>
<th>Controls (n = 335 232)</th>
<th>Relative Risk</th>
<th>Ï‡&lt;sup&gt;d&lt;/sup&gt;</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social Activity</td>
<td>Patients (n = 1659)</td>
<td>Siblings (n = 1659)</td>
<td>Concordant Pairs</td>
<td>Nonconcordant Pairs</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Score 1</td>
<td>105 (7.0)</td>
<td>45 (3.0)</td>
<td>6305 (1.8)</td>
<td>5 (5.1)</td>
<td>93 (94.9)</td>
<td>2.83</td>
</tr>
<tr>
<td>Score 2</td>
<td>421 (28.2)</td>
<td>328 (21.6)</td>
<td>54 996 (15.8)</td>
<td>110 (27.2)</td>
<td>295 (72.8)</td>
<td>1.72</td>
</tr>
<tr>
<td>Independent Behavior</td>
<td>Patients (n = 1659)</td>
<td>Siblings (n = 1659)</td>
<td>Concordant Pairs</td>
<td>Nonconcordant Pairs</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Score 1</td>
<td>22 (1.5)</td>
<td>15 (0.9)</td>
<td>1846 (0.5)</td>
<td>2 (9.5)</td>
<td>19 (90.5)</td>
<td>NC</td>
</tr>
<tr>
<td>Score 2</td>
<td>254 (17.0)</td>
<td>181 (11.9)</td>
<td>33 111 (9.5)</td>
<td>31 (15.4)</td>
<td>170 (84.6)</td>
<td>1.62</td>
</tr>
<tr>
<td>Functioning in School or Work</td>
<td>Patients (n = 1659)</td>
<td>Siblings (n = 1659)</td>
<td>Concordant Pairs</td>
<td>Nonconcordant Pairs</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Score 1</td>
<td>102 (6.8)</td>
<td>55 (3.6)</td>
<td>7921 (2.3)</td>
<td>5 (5.3)</td>
<td>90 (94.7)</td>
<td>2.23</td>
</tr>
<tr>
<td>Score 2</td>
<td>530 (35.5)</td>
<td>448 (29.5)</td>
<td>75 409 (21.6)</td>
<td>196 (38.2)</td>
<td>317 (61.8)</td>
<td>1.77</td>
</tr>
</tbody>
</table>

Abbreviation: NC, not computable.  
<sup>a</sup> Each social domain is rated on a 5-point scale, with lower scores indicating poorer functioning. A score of 1 represents very poor functioning, and a score of 2 indicates poor or weak functioning.  
<sup>b</sup> Comparison between distributions of the impairments in the sibling group with percentage impaired in the control group.

\( t_{1638.23} = -7.78, P < .001 \), lower IQ (\( t_{1577.29} = -19.27, P < .001 \)), and lower socioeconomic status (\( t_{1221.09} = -3.51, P < .001 \)). Siblings were comparable to controls in terms of educational level but had a significantly lower socioeconomic status (\( t_{1300.88} = -4.24, P < .001 \)).

Table 3 gives the number of patients, siblings, and controls with very poor (score, 1) and poor or weak (score, 2) community functioning scores. There was a clear dose-response relationship for both social activity and functioning in school or work with the RR for concordance in affected families increasing with increasing impairment. However, concordant pairs for the lowest scores were rare, and the RR for independent behavior could not be calculated.

The ICCs indicated a fair agreement between impairment scores of patients and their siblings (social activity: ICC, 0.244; 95% CI, 0.169-0.318; independent behavior: ICC, 0.257; 95% CI, 0.176-0.330; and functioning in school or work: ICC, 0.289; 95% CI, 0.212-0.359). The ICCs between control siblings were almost identical (social activity: ICC, 0.210; 95% CI, 0.081-0.321; independent behavior: ICC, 0.222; 95% CI, 0.095-0.344).
Discussion

With data from more than 700,000 individuals, this is, to our knowledge, the largest population-based study evaluating the developmental trajectories of impaired community functioning in schizophrenia. Our findings add to the existing knowledge of functional impairment trajectories in schizophrenia in 3 important ways.

First, our results indicate that not all domains of community functioning are equally impaired premorbidly in those who develop schizophrenia. Overall, cases were found to be significantly impaired in social activity and functioning in school or work, with impairments in the former being most severe.

Second, various impairments in community functioning may appear at different developmental stages. Impairments in social activity in cases began increasing and diverging from those of their unaffected siblings as early as 15 years before first hospitalization, stabilized for approximately 10 years, increased again 5 years before onset, and continued to increase thereafter. The magnitude of change in impairment in functioning in school or work was not significant, but our findings indicate a trend for functional decline starting 8 years before hospitalization, followed by impairments in independent behavior approximately 5 years before hospitalization.

Third, our results expand on previous research by revealing that impairments in social activity and functioning in school or work are familial. Siblings of patients exhibited small impairments compared with controls, and more severe deficits were seen in siblings of patients with more severe social impairments themselves. However, in contrast to patients, impairments in siblings did not increase progressively over time.

Although registry-based national cohort studies offer the unique advantage of prospectively following up large unbiased samples of individuals, they are not specifically designed to investigate schizophrenia and are therefore subject to some methodologic constraints. We cannot rule out that long-term absence of premorbid impairment in independent behavior is due to lower sensitivity of this scale. However, the largely comparable score distributions between community functions and the increasing impairment in independent behavior closer to hospitalization render it unlikely that differences in psychometric properties fully account for its discrepant findings. In addition, we were only able to use hospitalization to ascertain schizophrenia diagnosis, which may have led to underrepresentation of schizophrenia cases. However, because only 7% of individuals with schizophrenia in Israel are never hospitalized, it is unlikely that underrepresentation had a large effect on our results. Data were also only available in males, so future research in females is needed.

In addition, data on premorbid deterioration of community functioning are based on cross-sectional evaluations, thus not allowing subgroup- and within-subject analyses. Longitudinal studies are needed to confirm whether the decrease is indeed a function of time to illness onset and to examine whether subgroups exist within the 3 community functioning domains, as previously found in retrospective schizophrenia studies using the Premorbid Adjustment Scale.

Of the 3 functional domains, premorbid impairment in social activity was by far most pronounced. By illness onset, cases had social activity scores of more than 1 SD below healthy comparison controls. This finding adds to an increasing body of research that suggests that impairment in social activity is one of the most fundamental factors in the pathway to schizophrenia and clearly separates vulnerable individuals who develop a psychotic episode in the years before first hospitalization from those who do not. However, most previous studies investigating social activity in schizophrenia used either a retrospective or prodromal design, limiting conclusions that can be drawn about the temporal association between impairments and the start of psychotic symptoms due to recall bias or confounding by emerging symptoms. Our findings reveal that impairments in social activity are already present 15 years before first hospitalization.

There are a number of possible explanations for the progressive deterioration in community functioning found in this study. The first, most frequently posited model asserts that premorbid deficits in schizophrenia result from disturbances in the age-dependent neurodevelopmental processes. It has been argued that early adolescence, a time of substantial brain maturation, might be particularly critical and that the decrease in functioning reflects disrupted neurodevelopmental processes.

However, our findings suggest that an age-dependent model may not fully explain the decrease in social activity before first hospitalization. The stepwise decrease at 15 years and then again at 5 years before hospitalization suggests 2 critical periods, periods that may also be dependent on time to onset rather than just age. During the first decrease, schizophrenia cases may begin to diverge from their genetic potential, as indicated by the deviation from unaffected siblings. This divergence may suggest that the illness begins up to 15 years before first hospitalization.

The second crucial period, 5 to 8 years before hospitalization, arguably represents the start of the prodromal phase, which in some cases occurs years before the onset of psychosis. During this phase, community functioning may begin or continue to decrease and other symptoms increasingly appear. As argued previously, the accelerated decrease in functional impairment during this phase may be due to the emergence of symptoms in combination with increasingly demanding and complex social contacts as adult roles are taken on. Impaired social interaction, in turn, may further reinforce delusions because dysfunctional beliefs are not tested among peers. Longitudinal prospective research is needed to test this idea and to examine to what extent changes in functioning are driven by cognitive changes.

Regarding the familiality of impaired community functioning in schizophrenia, our findings support previous work that reveals that vulnerable families have decreased genetic functional potential. We found a small, but clear, dose-response relationship between the magnitude of impairments in social activity and functioning in school or work and level of familiality. In contrast, independent behavior was not at all familial, and deviations in this domain emerged only...
in the years preceding illness onset. This finding indicates that inability to behave independently may be an artifact of the developing illness. For example, patients and those around them may perceive their functioning as reduced as they begin to experience emerging, disabling, psychotic symptoms.

Conclusions

Overall, our findings indicate that examining community functioning as one global concept oversimplifies the complex nature of functional impairment and that different domains follow distinct trajectories in the years before first hospitalization. It is hoped that reducing the heterogeneity of the behavioral phenotype by parsing community functioning into separate domains will enable better identification of risk factors associated with schizophrenia. Genetic studies are needed to further disentangle familiality from heritability, to further understand the potentially unique pathophysiological pathways of these domains, and to determine whether functional anomalies make valuable candidates for sociogenomic research in schizophrenia.

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Study concept and design: Velthorst, Reichenberg, Fruchter, Ginat, Davidson, Weiser.

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Drafting of the manuscript: Velthorst, Reichenberg, Kaparà, Goldberg, Weiser.

Critical revision of the manuscript for important intellectual content: Reichenberg, Frumer, Ginat, de Haan, Davidson.

Statistical analysis: Velthorst, Reichenberg, Kaparà, Goldberg, Frumer.

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Study supervision: Reichenberg, Ginat, de Haan, Davidson, Weiser.

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REFERENCES


