



## Premorbid intra-individual variability in intellectual performance and risk for schizophrenia: A population-based study

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### Abstract

**Background:** Some, but not most, schizophrenia patients have below-average intelligence years before they manifest psychosis. However, it is not clear if those whose intelligence falls within-normal-range nevertheless have cognitive abnormalities. We examined the association between intra-individual variability in intellectual performance and risk for schizophrenia in individuals with normal IQ.

**Methods:** 555,326 adolescents, mandatory assessed by the Israeli Draft Board were followed up over 8 to 17 years for psychiatric hospitalization by means of the Israeli National Psychiatric Hospitalization Case Registry. Data were available on 4 intelligence sub-tests, and on behavioral and psychosocial variables. Variability was computed from the variance of the four intelligence tests' standardized scores.

**Results:** There was a significant monotonic association between increased intra-individual variability in intellectual performance and risk of schizophrenia in individuals with *within-normal-range IQ*. Individuals with the highest variability were 3.8 times more likely to have schizophrenia [95%CI: 2.32–6.08;  $p < 0.0001$ ] compared with individuals with the lowest variability. This association held after controlling for the effects of potential confounders.

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*Conclusions:* Despite within-normal-range premorbid IQ, apparently healthy adolescents who will later on manifest schizophrenia, nevertheless have cognitive abnormalities such as increased variability across intellectual tasks, possibly related to frontal lobe abnormalities.

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## 1. Background

Evidence exists indicating that as a group, individuals who later will be hospitalized for schizophrenia have intellectual deficits that predate the manifestation of psychotic symptoms and the assignment of diagnosis (Albee et al., 1964; David et al., 1997; Davidson et al., 1999; Jones et al., 1994). However, despite group mean differences between future patients and controls, in the majority of future schizophrenia patients mean test scores reflective of general intelligence (IQ) are within normal range (David et al., 1997; Reichenberg et al., 2006). If indeed cognitive abnormalities are a core feature of the illness (Andreasen, 1997; Goldman-Rakic, 1994) this would suggest that aspects of intellectual performance other than mean IQ scores might be relevant to the pathophysiology of the schizophrenic illness.

Several studies have reported large intra-individual variability across intellectual tasks (tests) in children with *normal IQ* whose parents were affected by schizophrenia (Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling and Cornblatt, 1987; Hanson et al., 1976; Rutschmann et al., 1980). Furthermore, intra-individual variation in intellectual functioning was the most effective variable in distinguishing “high-risk” individuals with normal IQ who later developed schizophrenia from those who remained non-psychotic (Ott et al., 1998).

Intra-individual variability in intellectual performance has been linked to neural dysconnectivity (Hultsch et al., 2000; Li and Lindenberger, 1999; Lindenberger and Baltes, 1997) of the frontal cortex (Stuss et al., 2003). In turn, cortico-cortical dysconnectivity of the frontal cortex has been proposed as relevant in the biology of schizophrenia (Bullmore et al., 1997; Gold and Weinberger, 1995; Weinberger and Berman, 1996). Faulty cortico-cortical neuronal connectivity has been postulated as a developmental deficit that may occur years prior to the manifestation

of psychosis and diagnosis of schizophrenia (Bullmore et al., 1997; Hoffman and McGlashan, 1994). Hence exploring intra-individual variability in intellectual performance in addition to mean IQ scores, in apparently normal, future schizophrenia patients, might better reflect the biological substrate of the intellectual impairment in schizophrenia.

To examine in future schizophrenia patients the relationship between intra-individual variability in intellectual performance and risk of adult-onset schizophrenia, we used data collected during the mandatory assessments performed at age 17 by the Israeli Draft Board. The data include assessments of intellectual functioning on almost all live births of Israeli-born Jews during 10 consecutive years. The Draft Board data was linked with psychiatric follow-up data provided by the Israeli National Psychiatric Hospitalization Case Registry.

## 2. Methods

### 2.1. Subjects

The study builds on the Israeli military Draft Board assessment of intellectual, medical, and psychiatric eligibility for service of the *unselected* population of Israeli-born Jewish adolescents at age 17 years and on the availability of the Israeli National Psychiatric Hospitalization Case Registry. The Draft Board population includes individuals who would be eligible for military service, as well as those who will be exempted due to medical, psychiatric, or social reasons. The study was approved by the relevant local IRB committees.

### 2.2. Standardized test measurements

The intellectual assessment carried by the Draft Board is conducted by college-age individuals who

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