Age at onset and cognitive functioning in schizophrenia

ANNA MARI TUULIO-HENRIKSSON, TIMO PARTONEN, JAANA SUVISAARI, JARI HAUkKA and JOUKO LÖNNQVIST

Background Impairments in cognitive functioning are common in schizophrenia, and the degree of impairment may be associated with the individual’s age at onset of the disorder.

Aims To examine the effect of age at onset on cognitive functioning using the California Verbal Learning Test, sub-tests from the Wechsler Memory Scale — Revised and sub-scales from the Wechsler Adult Intelligence Scale — Revised among families with schizophrenia.

Method The effect of age at onset on cognitive function in 237 people with schizophrenia from a population-based sample was examined using linear mixed effects models with family as the random effect, and age, gender, chronicity of the illness and number of affected first-degree relatives as fixed effects.

Results Impairment in verbal learning and memory was associated with earlier disease onset. No association was found for working memory or IQ.

Conclusions In patients with early-onset schizophrenia, verbal memory functions in particular should be taken into account in neuropsychological evaluation and efforts at remediation.

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Schizophrenia often has its onset in young adulthood, with severe negative consequences on education, social relationships and employment. Early onset has been related to poor clinical and psychosocial outcomes (DeLisi, 1992; Hoff et al., 1996; Eggers & Bunk, 1997). Moreover, age at onset may be associated with the severity of deficits in cognitive functions, such as learning (Jeste et al., 1998), attention and motor speed, understanding and producing speech (Hoff et al., 1996) and retrieval memory (Paulsen et al., 1995). Using a population-based sample of families in Finland, we set out to study whether the age at onset does associate with performance in attention and working memory, verbal learning and memory, and verbal and visuospatial ability. Following on from previous studies, we examined whether familial occurrence of psychosis, which has been associated with the age at onset (Suvisaari et al., 1998) and with the degree of cognitive deficits (Faraone et al., 2000; Tuulio-Henriksson et al., 2003), contributes to the effect of age at onset on the cognitive functions.

METHOD

Sample
The study sample was drawn from families including individuals with schizophrenia-spectrum disorders previously recruited for a population-based genetic epidemiological study, described in detail by Hovatta et al. (1997), Ekelund et al. (2000) and Paunio et al. (2001). This study identified 33731 persons (58% males) with a diagnosis of schizophrenia, schizoaffective psychosis or schizophreniform disorder from a cohort of all people born in Finland during the period 1940 to 1976 inclusive. Data on the diagnoses were derived from three nationwide computerised health care registers (the Hospital Discharge Register, the Free Medicine Register and the Pension Register) covering the years 1969–1998. Personal identification numbers, which code date of birth and gender, are unique for each individual; by linking the numbers of the affected subjects to the data on their family members derived from the National Population Register, we were able to construct pedigrees. The protocol was accepted by the ethics committee of the National Public Health Institute, and the study was granted permission by the Ministry of Social Affairs and Health.

Blood samples were drawn from 930 families identified from the registers; they comprised 281 families originating from a genetic isolate in the north-eastern part of Finland, with at least one child with schizophrenia, schizoaffective psychosis or schizophreniform disorder, and 649 families with at least two children with these disorders from the whole country. The collection of blood samples for the molecular genetic studies (Hovatta et al., 1997; Ekelund et al., 2001; Paunio et al., 2001) followed the recommendations given in the Declaration of Helsinki and its amendments. Consent for drawing the blood sample and for a future contact was documented in writing.

All available psychiatric case notes covering the patient’s whole illness history were collected for individuals with a diagnosis of schizophrenia, schizoaffective psychosis or schizophreniform disorder in any of the three national registers, and from whom a blood sample was drawn ($n=1410$). For each case, two psychiatrists, masked to family structure and register diagnosis, assessed independently the best-estimate lifetime diagnoses according to DSM-IV criteria (American Psychiatric Association, 1994). One of the assessors also filled out the Operational Criteria Checklist for Psychotic Illness (OPCRIT; McGuffin et al., 1991). Disagreements on the assessment of research diagnoses were reviewed by a third assessor and a consensus was reached.

All 281 families originating from the genetic isolate, and a sample of 50 families from the whole of Finland randomly selected from families who had previously given blood samples, were asked to participate in this study for detailed diagnostic information and neuropsychological examination. We began by contacting affected individuals (with the permission of their treating physician) to begin the informed consent process. After the affected person had given written consent, the
rest of the family were contacted and their consent requested, following a complete description of the study.

From the 275 families who gave consent, 411 patients and 561 family members were interviewed using the structured Clinical Interview for DSM-IV (SCID; First et al., 1997). All the interviewees received standardised training in the use of this instrument. The final consensus diagnoses were based on data collected from the records, the OPCRIT assessment and the SCID. The same neuropsychological test battery was administered to both affected and unaffected participants. For each family we endeavoured to interview the same number of affected and unaffected siblings, selecting those closest to the proband’s age and of the same gender, if possible.

We excluded 41 patients who had a diagnosis of a schizophrenia-spectrum disorder in the registers but who were assigned a consensus diagnosis of bipolar disorder, and 11 patients who received a consensus diagnosis of a non-psychotic disorder. Furthermore, we excluded 52 patients with schizoaffective disorder and 20 patients with schizophreniform disorder. This left us with 287 patients with schizophrenia. Of these, 35 either did not give a valid test performance or were untestable because of acute psychotic state or severe medical comorbidity. Reliable information about age at illness onset was not received for 11 patients, and 4 were excluded because of the very early age at onset (7–12 years). The cut-off point of age >12 years was chosen on the basis of previous research into childhood-onset schizophrenia (for a review, see Nicolson & Rapoport, 1999).

Our study thus comprised 237 persons with a diagnosis of schizophrenia from 208 families. Of the patients, 81 were women and 156 were men (P<0.001), reflecting a slight overrepresentation of males (66% v. 58% in the registers). The mean ages of women and men were similar, at about 45 years (Table 1). The course of the illness was chronic in 71% of women and 74% of men (data derived from the OPCRIT).

Information about the age at onset of schizophrenic illness was derived from the case notes as one of the OPCRIT items. The case notes were comprehensive and covered the in-patient and out-patient phases of the whole treatment history. The age at onset was defined as the earliest age at which medical advice was sought for occurrence of psychiatric symptoms, or at which the symptoms began to cause subjective distress or impair functioning.

The mean age at onset in the final sample was 23.2 years with no difference between women and men (Table 1), which is in line with a previous epidemiological study in Finland (Suvisaari et al., 1998). The IQ was estimated from four sub-scales from the Wechsler Adult Intelligence Scale – Revised (WAIS–R; Wechsler, 1981).

### Neuropsychological tests

The neuropsychological tests were administered to all participants in a fixed order. All examiners were psychologists or advanced psychiatric nurses extensively trained and supervised with the test battery. Experienced psychologists scored all the tests using the scoring rules detailed in the test manuals.

The test procedures have been described in detail by Tuulio-Henriksson et al. (2002). Auditory attention was assessed with the Digit Span Forward task, and verbal working memory with the Digit Span Backward task of the Wechsler Memory Scale – Revised (WMS–R; Wechsler, 1987). According to Finnish normative data, the test–retest reliability coefficients of the Digit Span sub-tests vary with age from 0.74 to 0.82 (Wechsler, 1996).

Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT; Delis et al., 1987), which examines recall and recognition of word lists over a number of trials. We report the following variables derived from the test: total recall (learning and memory), semantic clustering, learning from the beginning of the list (primacy) and from the end (recency), recall errors (perseverations and intrusions) and recognition memory (discriminability). No reliability data for Finnish subjects exist, but the split-half reliability of the CVLT is 0.77–0.86, according to the test manual (Delis et al., 1987).

Four sub-tests of the WAIS–R were used for measuring IQ. Verbal ability and abstraction were measured with the Vocabulary and Similarities sub-tests, respectively; the vocabulary test is considered to be the best single measure of general ability (Lezak, 1995). The Block Design and Digit Symbol sub-tests have a motor component, as the trials are timed; the former is a measure of visuospatial reasoning, and the latter measures psychomotor speed. According to Finnish normative data, the test–retest reliabilities for the Vocabulary, Similarities, Block Design and Digit Symbol measures are 0.89–0.95, 0.69–0.88, 0.78–0.83 and 0.82–0.86, respectively, depending on age (Wechsler, 1992).

### Statistical analyses

The analyses were made using linear mixed effect models separately for each neuropsychological test variable. Age at onset was treated in the models as a continuous variable, ranging from 13 to 44 years. In each model, family was included as a random effect, as from some families more than one family member was included. Age, gender, course of the illness (chronic v. episodic) and age at onset (years) were included as the fixed effects. Furthermore, we included in the models a continuous variable of the number of affected members in the family as a fixed effect in order to detect whether familial loading, measured by the number of first-degree relatives with a psychotic disorder, modifies the effect of the age at onset on cognitive functions. The information concerning the illness of the first-degree relatives was obtained from

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**Table 1** Demographic characteristics of the participants with schizophrenia (n=237)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gender</th>
<th>Age at illness onset, years: mean (s.d.)</th>
<th>Education, years: mean (s.d.)</th>
<th>Estimated IQ: mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female, %</td>
<td>34</td>
<td>23.2 (5.7)</td>
<td>45.4 (8.4)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>23.0 (5.7)</td>
<td>45.0 (7.5)</td>
<td>45.2 (7.8)</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>22.3 (5.7)</td>
<td>45.0 (7.5)</td>
<td>45.2 (7.8)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>23.2 (5.7)</td>
<td>45.0 (7.5)</td>
<td>45.2 (7.8)</td>
</tr>
</tbody>
</table>
the national registers. In addition, we remodelled all test variables with the above-mentioned random and fixed effects plus duration of the illness (tertiles from age at onset subtracted from the age at testing, in years). All analyses were two-tailed, and the probability level of $P < 0.05$ indicated statistical significance. Analyses were performed using the S-Plus statistical software, version 3.4 (S-Plus, 1996).

RESULTS

Effect of age at onset

In the mixed linear effect models, lower scores on four cognitive functions were significantly associated with earlier age at onset (Table 2). These functions were verbal learning and memory, assessed as total recall from trials 1 to 5 in the CVLT (coefficient for the effect of how much each increasing year in the age at onset changes the value of the test score 0.483, s.d. = 0.14, $P = 0.002$); using semantic clusters as a learning strategy (effect coefficient 0.023, s.d. = 0.01, $P = 0.02$); recognition memory (effect coefficient 0.256, s.d. = 0.05); and making errors during recall (intrusions) (effect coefficient $-0.033$, s.d. = 0.01, $P = 0.007$).

Fixed-effect contributions

Course of the illness (chronic v. episodic) contributed to the measured IQ functions (all $P$ values $< 0.03$). Chronicity also showed a significant effect on verbal learning and memory (effect coefficient $-6.245$, s.d. = 1.8, $P < 0.001$), semantic clustering (effect coefficient $-0.287$, s.d. = 0.11, $P = 0.02$), delayed verbal memory (effect coefficient $-1.723$, s.d. = 0.48, $P < 0.001$), recognition memory (effect coefficient $-5.300$, s.d. = 1.62, $P = 0.002$) and intrusions (effect coefficient 0.348, s.d. = 0.14, $P < 0.02$), but it did not eliminate the effect of age at onset on these variables. Including duration of the illness in the models did not change the results, and this variable did not contribute significantly to any of the measured cognitive functions. The number of affected first-degree relatives in the family showed a significant effect on visual working memory (effect coefficient $-0.27$, s.d. = 0.13, $P = 0.04$), verbal ability (effect coefficient $-1.80$, s.d. = 0.83, $P = 0.04$) and processing speed (effect coefficient $-1.31$, s.d. = 0.61, $P = 0.03$).

DISCUSSION

An association exists between age at onset of schizophrenia and impaired performance in verbal learning and memory tasks. Those younger at disease onset recalled fewer words in verbal list learning, and while recalling made less use of semantic clusters, that is they did not effectively group the words in the list into categories. Furthermore, they performed worse in recognition, and more frequently made intrusive errors (i.e. produced more words that were not in the original list) than those with a later onset. However, earlier age at onset was not associated with lower scores on working memory tasks or on tests measuring IQ functions.

Familial loading, measured as the number of affected first-degree relatives in the family, did not contribute to the effect of age at onset on cognitive functioning, but showed a significant effect on visual working memory, verbal IQ and processing speed. Chronicity contributed strongly to the cognitive test scores, but did not eliminate the significant effect of age at onset from the verbal learning and memory functions.

Strengths and limitations of the study

To our knowledge, this study is the first to examine how the age at onset is associated with cognitive function, using a large population-based sample of families of people with schizophrenia. Furthermore, we controlled for the impact of familial loading. This study design allowed us to take into account intrafamilial features in the neuropsychological test data. Our analyses showed that scores in visual working memory and verbal IQ were worse when there were more affected first-degree relatives in the family, irrespective of the age at onset. This result provides further support for the evidence of genetic influence on visual working memory deficits in families with individuals with schizophrenia that has been reported in previous studies (Park et al, 1995; Cannon et al, 2000; Tuulio-Henriksson et al, 2002).

Since the participants with schizophrenia in our study sample had a wide range of age, some of the results might reflect normal deterioration of cognitive

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### Table 2 Neuropsychological test results and effect of age at onset of schizophrenia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test score</th>
<th>Effect of age at onset, per year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (s.d.)</td>
<td>Coefficient (s.d.) P</td>
</tr>
<tr>
<td>Attention and working memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory attention</td>
<td>6.0 (1.8)</td>
<td>0.022 (0.02) 0.31</td>
</tr>
<tr>
<td>Verbal working memory</td>
<td>4.9 (1.7)</td>
<td>0.028 (0.02) 0.16</td>
</tr>
<tr>
<td>Visual attention</td>
<td>7.4 (1.8)</td>
<td>0.019 (0.02) 0.38</td>
</tr>
<tr>
<td>Visual working memory</td>
<td>6.5 (2.3)</td>
<td>0.023 (0.03) 0.38</td>
</tr>
<tr>
<td>Verbal memory functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal learning and memory</td>
<td>33.8 (12.6)</td>
<td>0.483 (0.14) 0.0002</td>
</tr>
<tr>
<td>Semantic clustering</td>
<td>7.2 (6.3)</td>
<td>0.023 (0.01) 0.02</td>
</tr>
<tr>
<td>Discriminability</td>
<td>86.6 (11.6)</td>
<td>0.256 (0.13) 0.05</td>
</tr>
<tr>
<td>Primacy</td>
<td>26.3 (11.4)</td>
<td>–0.095 (0.14) 0.49</td>
</tr>
<tr>
<td>Recency</td>
<td>32.0 (12.9)</td>
<td>–0.159 (0.15) 0.30</td>
</tr>
<tr>
<td>Delayed verbal memory</td>
<td>7.2 (3.5)</td>
<td>0.067 (0.04) 0.10</td>
</tr>
<tr>
<td>Perseverations</td>
<td>0.5 (0.4)</td>
<td>0.001 (0.01) 0.90</td>
</tr>
<tr>
<td>Intrusions</td>
<td>0.7 (0.4)</td>
<td>–0.033 (0.01) 0.007</td>
</tr>
<tr>
<td>IQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal ability</td>
<td>31.4 (14.2)</td>
<td>0.195 (0.14) 0.19</td>
</tr>
<tr>
<td>Abstraction</td>
<td>20.2 (6.6)</td>
<td>0.146 (0.07) 0.06</td>
</tr>
<tr>
<td>Visuospatial reasoning</td>
<td>20.7 (10.6)</td>
<td>0.103 (0.12) 0.40</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>29.2 (12.5)</td>
<td>0.086 (0.12) 0.49</td>
</tr>
</tbody>
</table>

Linear mixed effects models with family as a random effect, and fixed-effect adjustments for age, gender, chronicity of the illness and number of affected first-degree relatives.

1. Logarithmised for normality.
function with increasing age. However, we
controlled for the effect of age in the analy-
sis. Moreover, these participants were not
people experiencing a first episode, but
individuals with an often chronic course of
illness who might have been exposed to
noxious effects of the illness or medication,
with negative effects on cognitive functions.
However, by controlling for chronicity, and
in additional models also for the duration
of the illness in the analysis, we took at
least partial account on these potential
confounds. Besides, duration of the illness
may not be associated with the severity of
cognitive deficits in schizophrenia (Heaton
et al., 2001).

Our definition of familiality was based
on the number of affected first-degree rela-
tives with a psychotic disorder, instead of
using the more sophisticated calculations
presented by Verdoux et al. (1996) or
Lawrie et al. (2001). However, since the
majority of the families under study had
at least two affected family members, and
therefore represented familial schizo-
phrenia, we considered that it was adequate
to use the number of affected family mem-
bers as a measure of familial loading in
the analyses. Furthermore, the method in-
troduced by Lawrie et al. (2001) would have
assumed spousal correlation to be 0, but
this was not always the case in the genetic
isolate included in our study sample.

Verbal memory as a vulnerable
cognitive function in early-onset
schizophrenia

More severe learning and memory impair-
ments, as measured by the total recall score
on the CVLT, have been associated with
earlier onset of schizophrenia (Jeste et al.,
1998). In accordance with the study by
Jeste et al. (1998), cognitive functions related
to verbal learning and memory,
particularly to initial encoding, showed
the strongest associations of interest in
our study. This does not imply a relative
impairment of verbal learning and memory
compared with the other measured cogni-
tive functions. However, the association
between age at disease onset and verbal
learning and memory remained even in
the presence of chronicity, which accounted
for most of the variance of the other cogni-
tive functions. Turetsky et al. (2002) identi-
fied three memory-delineated subtypes
of schizophrenia: based on verbal memory
impairment (measured using the CVLT)
these subtypes were defined as those
conforming to the phenotypes of cortical
and subcortical dementia, and those with
no impairment. Patients in the group
in which the memory deficits (poor total
recall scores on the CVLT and frequent
intrusive errors) were similar to those
observed in cortical dementia had an earlier
onset of disease than the unimpaired group
(Turetsky et al., 2002). Our results support
these findings.

Furthermore, patients with prodromal
signs of schizophrenia have been found to
show compromised verbal memory (free
recall of a word list) measured with the
Auditory Verbal Learning Test, which is
similar to the CVLT used in our study
(Hambrecht et al., 2002). Verbal learning
and memory functions may be particularly
vulnerable to the developmental process
leading to schizophrenia. The poor psycho-
social outcome associated with early onset
of schizophrenia (Schulte et al., 2000) may
be influenced by impairment in verbal
learning and memory functions in particu-
lar. The deficits associated with verbal
memory functions, inevitably undermining
social adaptation and educational possibili-
ties, may predispose individuals to an
earlier onset of schizophrenia.

IQ and age at onset

In line with the prospective study by Fuller
et al. (2002), we found no association
between age at onset and measures of IQ.
It may be that low IQ, although a risk fac-
tor for schizophrenia (David et al., 1997),
is not linked with age at onset. However,
our cross-sectional study comprised mostly
patients with chronic schizophrenia,
and chronicity contributed strongly to the test
scores in the four WAIS–R scales. The IQ
measures might not have been sensitive
eough to show association with age at
onset in the presence of a strong contribu-
tion of chronicity. In a large study of mili-
tary conscripts, an association was found
between poor intellectual functioning at
18 years of age and onset of schizophrenia
about 5 years later (Gunnell et al., 2002).
However, when IQ was controlled for in
a study of adolescent patients with recent
onset of schizophrenia, verbal and general
memory impairments were particularly
observed (Kravariti et al., 2003).

Implications of the study

Our results are in agreement with previous
studies showing that an early age at onset
of schizophrenia is associated with specific
rather than global cognitive deficits. In
our population-based sample of patients
with schizophrenia, this association was
found in the verbal learning and memory
functions. Verbal memory deficits – known
to be highly associated with functional out-
come in schizophrenia (Green, 1996) –
should particularly be taken into account
in the neuropsychological evaluation and
efforts at remediation in patients with
early-onset disorder. Prospective research
on verbal memory functions during pro-
dromal phases, and on the predictive value
of impairments for disease outcome, is
urgently required.

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this study. The field workers who collected the data
and the research clinicians who read through the
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Longitudinal assessment of premorbid cognitive
functioning in patients with schizophrenia through
examination of standard scholastic text performance.
The nature of learning and memory impairments in families in Finland reveals susceptibility loci on 14:18–1428.

Neuropsychological assessment is important for planning rehabilitation efforts aimed at preventing a poor psychosocial outcome.

The participants were not first-episode patients, and it is not known whether they had verbal memory impairment at the time of disease onset.

As the mean age of the patients was about 45 years, our results may partly reflect the effects of ageing, although we controlled for the effect of age.


Correspondence: Annamari Tuulio-Henriksson, National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, Finland
Age at onset and cognitive functioning in schizophrenia
Annamari Tuulio-Henriksson, Timo Partonen, Jaana Suvisaari, Jari Haukka and Jouko Lönnqvist
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