1. Tieteellinen esitys:

Separable developmental trajectories in schizophrenia from womb to grave: results from the Northern Finland 1966 Birth Cohort.

2. Voidaanko hoitoyhteisömallilla vaikuttaa skitsofrenian kulkuun?

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Professor of Psychiatry

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Aims of this presentation:

To present pre- and postmorbid developmental pathways to schizophrenic psychosis within Northern Finland 1966 Birth Cohort:

1. Premorbid risk factors
2. Brain morphology
3. Pathways to death, predictors of mortality.
4. Global view, systems model
The Northern Finland 1966 Birth Cohort

- 12,058 subjects born in 1966 (96% of all births in the region) with low attrition (about 10%) followed over 40 years
- Developmental data supplemented by a special examination at second trimester of pregnancy and repeated extensively at ages 1, 16, 31, 34 and 43.
- In addition extensive register data is used (morbidity, mortality, drugs, education, occupation etc)
- Two extensive field studies for about 140 psychoses and 100 controls (brain imaging, genetics, cognition, clinical course) in 1999-2001 and 2008-2010
Aims of this presentation:

To present pre- and postmorbid developmental pathways to schizophrenic psychosis:

1. Premorbid risk factors: traditional precursors
2. Brain morphology
3. Pathway to death
4. Global view, systems model
Table 1. Different statistics indices to most essential risk factors of schizophrenia in the Northern Finland 1966 Birth Cohort. Statistically significant risk factors are described in bold. Last review in Isohanni et al World Psychiatry 2006. Estimates and predictive power low.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Crude statistics</th>
<th>Adjusted* odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.8</td>
<td>1.2-2.7</td>
</tr>
<tr>
<td>Birth weight &lt;2500g</td>
<td>2.2</td>
<td>1.1-4.6</td>
</tr>
<tr>
<td>Gestational age &lt;37 weeks</td>
<td>1.0</td>
<td>0.4-2.4</td>
</tr>
<tr>
<td>Perinatal brain damage</td>
<td>5.7</td>
<td>2.6-12.5</td>
</tr>
<tr>
<td>One or more as above obstetric complications</td>
<td>1.7</td>
<td>0.9-3.0</td>
</tr>
<tr>
<td>Central nervous system infection</td>
<td>2.9</td>
<td>1.1-8.0</td>
</tr>
<tr>
<td>Unwanted pregnancy</td>
<td>2.0</td>
<td>1.2-3.2</td>
</tr>
<tr>
<td>Not normal school grade</td>
<td>4.4</td>
<td>2.7-7.1</td>
</tr>
<tr>
<td>Late learning to stand 12 or later (months)</td>
<td>2.0</td>
<td>1.4-3.0</td>
</tr>
<tr>
<td>Late learning to walk 12 or later (months)</td>
<td>1.9</td>
<td>1.2-3.0</td>
</tr>
<tr>
<td>Speaking at the age of 1 year</td>
<td>1.3</td>
<td>0.8-1.9</td>
</tr>
<tr>
<td>No words</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day time wetting at the age of 1 year</td>
<td>1.2</td>
<td>0.7-2.1</td>
</tr>
<tr>
<td>Wet every day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night wetting at the age of 1 year</td>
<td>1.3</td>
<td>0.9-2.0</td>
</tr>
<tr>
<td>Wet every night</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potty trained at the age of 1 year</td>
<td>1.8</td>
<td>1.2-2.6</td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR= Odds ratio. CI= Confidence interval. R² = Nagelkerke R²; indicates how much variation is explained. PAR% = Population attributable risk percentage. * Adjusted with all variables in the table.
But risk factors are not so simple…

- Although early learning at age 1 "protects" or predicts low incidence of schizophrenia, some of early learners get ill.
- What is their clinical picture and outcome? Better as was their learning at age 1? No!
- Early learners with schizophrenia had more severe clinical course (Jääskeläinen et al Sch Res 2008).
- Risk factor of schizophrenia is not necessarily a prognostic factor!
Aims of this presentation:

To present pre- and postmorbid developmental pathways to schizophrenic psychosis:

1. Premorbid risk factors and endophenotypes
2. Brain morphology
3. Mortality
4. Global view, systems model
Our aim in imaging study

• To model path of neurodevelopment in psychosis over the lifespan
• Described in detail by Tanskanen et al (Sch Res 2004, Sch Bull 2008) or Ridler (PNAS 2006)
• Use different measures at different time points: at age 34 and (now in progress) 43
  – infant motor development at about age 1 years
Study 1: Grey Matter Deficits and Excesses. Northern Finland 1966 Birth Cohort Study

Relative deficits (blue and purple) and relative excesses (red and yellow) in regional grey matter were identified in patients with schizophrenia, relative to healthy comparison subjects. Grey matter deficits were found bilateral in the cerebellum, brain stem, claustrum, thalamus, insula, middle and inferior frontal, superior temporal, fusiform, parahippocampal, precentral, posterior cingulate, lingual gyri and cuneus; unilaterally in the left putamen, anterior cingulate, subcallosal, superior frontal, tranverse temporal gyri and precuneus; and in the right caudate and postcentral gyrus. Grey matter excesses were found bilaterally in the caudate, anterior cingulate, medial frontal gyri; and unilaterally in left putamen, pallidus and middle frontal gyrus (Tanskanen et al, Sch Bulletin 2008)
Study 2: Do they progress?

Within schizophrenic group duration of illness and grey matter association areas. There was a significant correlation between the duration of illness and the volume of “critical” areas identified as deficits (in the case-control comparison) in patients with schizophrenia (Tanskanen et al, Sch Bulletin 2008)
Study 4: Can we predict adult brain morphology at age 1?

• We have identified evidence of structural and psychological dysfunction in a distributed network involving a fronto-striatal-cerebellar circuit in schizophrenia.
• We were able for first time to demonstrate that the normal relationship between infant development at age 1 and adult brain structure 34 years later is disturbed in schizophrenia (“developmental dysmetria”).
• Brain development is different in schizophrenia.
A) Infant motor development (IMD summary score, x-axis) at age predicts gray matter density at age 34 years in bilateral premotor cortex (y-axis), and B) white matter density in parietal and frontal lobes (y-axis), in non-psychotic subjects (solid line) but not people with schizophrenia (broken line).
Aims of this presentation:

To present pre- and postmorbid developmental pathways to schizophrenic psychosis:

1. Premorbid risk factors
2. Brain morphology
4. Global view, systems model: how to describe and summarise all pieces of information?
Number and percent of suicides and odds ratio for suicide in different diagnostic groups by school performance assessed using mean school marks at the age of 16 years in the Northern Finland 1966 Birth Cohort. School marks range from 4 (fail) to 10 (excellent) (Alaräisänen et al Acta Psych Scand 2006)

<table>
<thead>
<tr>
<th>Diagnostic groups</th>
<th>Mean school marks under 8.5</th>
<th>Good school performance (8.5 and over)</th>
<th>Hazard ratio* (unadjusted)</th>
<th>Hazard ratio† (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suicides/all</td>
<td>%</td>
<td>Suicides/all</td>
<td>%</td>
</tr>
<tr>
<td>All non-psychotic (n = 10 546)</td>
<td>43/8470</td>
<td>0.5</td>
<td>2/2076</td>
<td>0.1</td>
</tr>
<tr>
<td>No diagnosis† (n = 10 242)</td>
<td>31/8189</td>
<td>0.4</td>
<td>2/2053</td>
<td>0.1</td>
</tr>
<tr>
<td>Non-psychotic disorder§ (n = 304)</td>
<td>12/281</td>
<td>4.3</td>
<td>0/23</td>
<td>0</td>
</tr>
<tr>
<td>All psychoses (n = 149)</td>
<td>6/127</td>
<td>4.7</td>
<td>4/22</td>
<td>18.0</td>
</tr>
<tr>
<td>Other psychosis (n = 54)</td>
<td>1/47</td>
<td>2.1</td>
<td>2/7</td>
<td>26.6</td>
</tr>
<tr>
<td>Schizophrenia (n = 95)</td>
<td>5/80</td>
<td>6.3</td>
<td>2/15</td>
<td>13.3</td>
</tr>
<tr>
<td>Total</td>
<td>49/8597</td>
<td>0.6</td>
<td>6/2098</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Test for interaction between diagnosis (all psychoses vs. no diagnosis and school mark): Wald chi-square test 6.70, P = 0.01.

*Crude hazard ratio for suicide, reference group is school mark under 8.5.
†Adjusted (gender, age of onset and social class at 1980 in psychoses; gender and social class at 1980 in non-psychotic group) hazard ratio for suicide, reference group is school mark under 8.5.
‡Never hospitalized due to any psychiatric disorder.
§Hospitalized due to non-psychotic psychiatric disorder.
## Pathways to Suicide in Schizophrenia

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TPH A779C/A218C, 5-HT2A, 5-HTT, family history of suicide</td>
<td>Problems in development, Long duration, many exacerbations, chronic course</td>
<td>Impulsiveness, hostility, aggression, alcohol abuse, Poor adherence to treatment</td>
<td>Good functioning, e.g. good school performance, Decline in functioning</td>
<td>Poor psychosocial support, Failure to recognise suicidality</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Good insight, fear of mental disintegration</td>
<td>Alcohol/substance abuse</td>
<td>Post-psychotic depression</td>
<td>EP side effects/akathisia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbid depressive syndrome</td>
<td>Hopelessness</td>
<td>Impulsive suicidal acts</td>
<td></td>
<td>Poor adherence to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- MAO-A
- COMT 158 Val/Met
- COMT 158 Met/Met
- TPH A779C/A218C
- 5-HTT
Aims of this presentation:

To present pre- and postmorbid developmental pathways to schizophrenic psychosis:

1. Premorbid risk factors
2. Brain morphology
4. Global view, systems model: how to describe and summarise all pieces of information?
Schizophrenia: major scientific mystery

• Systems theory is an attempt to integrate and to create wholes out of parts.

• In the following model we present main elements of systems theory and adapt them to schizophrenia, as well as present our model on systems view in schizophrenia (Isohanni et al in review).
Figure 1  Descriptive life span and multilevel model of schizophrenic psychoses.
Figure 1. Descriptive life span and multilevel model of schizophrenic psychoses.

RISK GENES
- COMT (22q11)
- DTNBP (6p22.3)
- RGS4 (1q22)
- ARG1 (1p21.3)
- C5 (1q42)
- MAOA (2q24.3)
- BDNF (11p15)
Figure 1          Descriptive life span and multilevel model of schizophrenic psychoses.

**GENETIC FACTORS**
- DNA methylation
- Histone modification

**RISK GENES**
- COMT (22q11.1)
- DTNBP (6p22.3)
- RGS4 (1q22)
- NRGI (8p22.11)
- DISCI (1q42)
- DAOC (2q23)
- BDNF (11p13)

**ILLNESS COURSE**
- Birth
- Premorbid period
- Illness onset
- Prodromal period
- Episode onset
- Clinical course & outcome of schizophrenia

**LIFE COURSE**
- Pregnancy
- Childhood, youth
- Adolescence, early adulthood
- Adulthood, ageing
RISK GENES
- COMT (22q11.1)
- DTNBP (6q22.3)
- GAB1 (1q22)
- HARS (1q21.1)
- H2Q1 (1q42)
- MAO (Xq22/q71/13q23)
- RNF (11p13)

GENETIC FACTORS
- DNA methylation
- Histone modification

ENDOPHENOTYPES OF SCHIZOPHRENIA
- Reduced or altered brain volumes
- Abnormal fMRI activation patterns
- Reduced sensorimotor gating: PPI, P50 ERP
- Eye movement abnormalities
- P300 ERP abnormalities

PATHOPHYSIOLOGY OF CNS SYSTEMS
- Molecular abnormalities
- Functional polymorphism in genes coding neurotransmitters
- Altered cell development
- Altered connectivity
- Deficits in brain reward and reinforcement systems
- Impairments in neuronal synchronization
- Dysfunctions in neuronal firing pattern

ENDOPHENOTYPES
- Reduced or altered brain volumes
- Reduced sensorimotor gating: PPI, P50 ERP
- Eye movement abnormalities
- P300 ERP abnormalities
- Eye movement abnormalities

Figure 1: Descriptive life span and multilevel model of schizophrenic psychoses.
Figure 1 Descriptive life span and multilevel model of schizophrenic psychoses.
Figure 1

Descriptive life span and multilevel model of schizophrenic psychoses.
Figure 1 Descriptive life span and multilevel model of schizophrenic psychoses.
Pros and cons of this kind of model

**Pros**

- **Didactically** useful; may help communication
- Demonstrates **complexity**
- Demonstrates **important aspects linked to time**: eg. duration of untreated psychosis, duration of drug treatment, duration of acute psychosis and remissions
- Demonstrates **life span view** and poorly studied areas.

**Cons**

- Easily **superficial**: not unity theory. **Submodels** needed.
- Integration of many theories and findings around schizophrenia, and systems theory **just beginning**
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**UQueensland:** John McGrath, Joy Welham

**UTSW, Dallas:** Carol Tamminga, Subroto Ghose, Elena Ivleva

**UGeorgia:** Brian Kirkpatrick, Brian Miller

**Finland:** about 11000 Cohort members and their relatives
2. Voidaanko hoitoyhteisömallilla vaikuttaa skitsofrenian kulkuun?

- osa sosiaalipsykiatrista innostusta 1960-90
- vuorovaikutus, jaettu päätöksenteko, psykoedukaatio
- Sopimusvuori ry, psykoosipotilaiden hoitoyhteisöt, vanhusten hoitoyhteisöt
- Tieteellisiä julkaisuja, oppikirjoja
- Mitä jäi käteen?
  - Lievitti psykoosin traumaattisuutta
  - Antipsykoottien annostelu putosi jopa 2/3: etu vai haitta?
  - Vähensi laitoshoidon haittoja
  - Pitkäaikaishyöty, kustannusvaikuttavuus: ei tietoa
  - Hyöty hitaasti, kun tauti lievenee ikääntymisen myötä?