Lost in translation

Eero Vasar
Estonian Academy of Sciences
Translational medicine

• **Translational medicine** (also referred to as translational science) is a discipline within biomedical and public health research that aims to improve the health of individuals and the community by “translating” findings into diagnostic tools, medicines, procedures, policies and education.
Kenneth J. Pienta, 2011

Diagram:
- Discovery
  - Bench to bedside - T1
- Approved Application (Patient)
  - Application and guidelines - T2
  - Dissemination – T3
- Practice (Community)
  - Outcomes / evaluation - T4
Translational research: Crossing the valley of death (D. Butler, 2008)

17 years from discovery to implementation
Translational research: Crossing the valley of death (D. Butler, 2008)
Is there any chance to think that scientific excellence is possible without the brain?

Whole brain
1508.91 ± 299.14 g
170.68 ± 13.86 B cells
| 86.66 ± 8.12 B neurons |
| 84.61 ± 8.83 B non-neur |
| 0.99 non-neur/neurons |

Cerebral cortex (GM+WM)
1232.93 ± 233.68 g
77.18 ± 7.72 B cells
| 16.34 ± 2.17 B neurons |
| 60.84 ± 7.02 B non-neur |
| 3.76 non-neur/neurons |

Rest of brain
117.66 ± 45.42 g
8.42 ± 1.50 B cells
| 0.69 ± 0.12 B neurons |
| 7.73 ± 1.45 B non-neur |
| 11.35 non-neur/neurons |

Cerebellum
154.02 ± 19.29 g
85.08 ± 6.92 B cells
| 69.03 ± 6.65 B neurons |
| 16.04 ± 2.17 B non-neur |
| 0.23 non-neur/neurons |

Figure 2. Absolute mass, numbers of neurons, and numbers of nonneuronal cells in the entire adult human brain. Values are mean ± SD and refer to the two hemispheres together. B, billion.
Emil Kraepelin and *dementia praecox*: an example of translational medicine

- The nonspecific concept of madness has been around for many thousands of years and schizophrenia was only classified as a distinct mental disorder by E. Kraepelin in 1887.
- He was the first to make a distinction in the psychotic disorders between what he called *dementia praecox* and manic depression. E. Kraepelin believed that dementia praecox was primarily a disease of the brain, and particularly a form of dementia. E. Kraepelin named the disorder *dementia praecox* (early dementia) to distinguish it from other forms of dementia (such as Alzheimer's disease) which typically occur late in life. He used this term because his studies focused on young adults with dementia.
- E. Kraepelin also observed that this syndrome often follows a progressive course without remission, leading ultimately to a dramatic deterioration of intellect.
New Anatomical Theatre: Emil Kraepelin and birth of modern psychopharmacology
Example of translational research
Ueber die Beeinflussung
einfacher psychischer Vorgänge
durch einige Arzneimittel.

Experimentelle Untersuchungen

von

Dr. Emil Kraepelin,
Professor der Psychiatrie in Heidelberg.

Mit einer Curventafel.

Jena,
Verlag von Gustav Fischer.
1892.
E. Bleuler and schizophrenia

• The Swiss psychiatrist, Eugen Bleuler, coined the term, "schizophrenia" in 1911. He was also the first to describe the symptoms as "positive" or "negative."

• E. Bleuler changed the name to schizophrenia as it was obvious that Krapelin's name was misleading as the illness was not a dementia (it did not always lead to mental deterioration) and could sometimes occur late as well as early in life.
E. Bleuler and schizophrenia

- E. Bleuler emphasized the notion of a fundamental disorder of thought and feeling, which every psychiatrist for decades learned as the four ‘a’s—disturbances of associations, affect, ambivalence and autistic isolation.
Schizophrenia

• Schizophrenia is perhaps the most devastating disorder of humankind. It strikes about 1% of the population worldwide, and it seems to affect men slightly more frequently and severely than it does women.

• In addition, another 2-3% of the general population have schizotypal personality disorder, which is often considered to be a milder form of the disease because patients do not manifest overtly psychotic behavior.
The negative impact of psychiatric disorders

- The negative impact of psychiatric disorders is steadily rising in the modern society. The recent study, involving the countries of European Union, has established that in every year over a third of the total population suffers from mental disorders (Wittchen et al., 2011). The prevalence of most difficult mental disorders, including major depression (6.9%), psychotic disorders (1.2%) and bipolar disorder (0.9%), has reached to the level of 9%.

- Psychopharmacological treatment for these mental disorders has been around almost 60 years. Indeed, considerable success has been achieved in the development of new molecules for treatment of these patients. The extrapyramidal side effect profile of second-generation antipsychotic drugs is milder compared to haloperidol and chlorpromazine. The occurrence of severe depressive symptoms due to the antipsychotic medication is not as disturbing with the second-generation drugs as established for chlorpromazine or reserpine.
The negative impact of psychiatric disorders

• Sustained recovery occurs in less than 14% within the first five years following a psychotic episode. Longer-term outcomes may be marginally better: a large international 25-year follow-up study reported an additional 16% with late-phase recovery. Throughout Europe, less than 20% of people with schizophrenia are employed.

• A large US study found nearly 20% homeless in a one-year follow up. And a recent report from a patient advocacy group reported that in the US those with serious mental illness were three times more likely to be found in the criminal justice system than in hospitals.
### Summary of long-term clinical outcome studies in schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Years of follow-up</th>
<th>Number of patients</th>
<th>Good clinical outcome (%)</th>
<th>Poor clinical outcome (%)</th>
<th>Social recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciompi 1980</td>
<td>37</td>
<td>289</td>
<td>27</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>Bleuler 1978</td>
<td>23</td>
<td>208</td>
<td>20</td>
<td>24</td>
<td>51</td>
</tr>
<tr>
<td>Bland &amp; Orne 1978</td>
<td>14</td>
<td>90</td>
<td>26</td>
<td>37</td>
<td>65</td>
</tr>
<tr>
<td>Salokangas 1983</td>
<td>8</td>
<td>161</td>
<td>26</td>
<td>24</td>
<td>69</td>
</tr>
<tr>
<td>Shepherd et al., 1989</td>
<td>5</td>
<td>49</td>
<td>22</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>
The negative impact of psychiatric disorders

- However, the emerging of metabolic syndrome (including insulin resistance, lipid abnormalities, and weight gain) in patients being medicated with the second-generation antipsychotic drugs (olanzapine) is a new obstacle. Nevertheless, the recent study of Tiihonen et al. (2009) has demonstrated that although the proportional use of second-generation antipsychotic drugs rose from 13% to 64% during follow-up, the gap in life expectancy between patients with schizophrenia and the general population did not widen between 1996 (25 years), and 2006 (22.5 years).

- However, no major progress has been accomplished either, because the life expectancy of patients is still more than 20 years shorter than in the general population. Moreover, a significant number of patients, suffering from schizophrenia, do not benefit from using of antipsychotic drugs and their fate is not much different from dementia praecox described by Emil Kraepelin 120 years ago.
Schizophrenia

• Positive symptoms
• Negative symptoms
• Cognitive deficits
Positive symptoms of schizophrenia

- Loss of reality testing
- Delusions
- Hallucinations
- Disorganized speech/formal thought disorder
- Disorganized/bizarre/catatonic behaviour
- Memory disturbances
- Dopamine driven
Negative symptoms

- Poverty of speech – restriction in the amount of spontaneous speech and in the information contained in speech (alogia)
- Flattening of affect – restriction in the experience and expression of emotion
- Anhedonia-asociality – inability to experience pleasure, few social contacts and social withdrawal
- Avolition-apathy – reduced drive, energy and interest
- Attentional impairment – inattentiveness at work and interview
Cognitive deficits

• In addition to positive and negative symptoms, it has become increasingly clear that morbidity in schizophrenia is seriously affected by cognitive deficits, especially in tasks that require executive function, working memory, or attention (Green et al., 2000; Green and Nuechterlein, 2004).
Cognitive deficits

• While positive and negative symptoms of schizophrenia can fluctuate, cognitive deficits remain relatively stable, and are already apparent in first-episode patients who have never received antipsychotic medicines. **Cognitive deficits are found in the biological relatives of subjects with schizophrenia**, suggesting that aspects of cognition impaired in schizophrenia may be under specific genetic control, and therefore, serve as informative endophenotypes in the genetic analysis of schizophrenia. **Cognitive dysfunction has been recognized as a core feature of schizophrenia, leading to impairment of skills and diminished functional capacity.**
Genetics

• One approach that could separate cause from effect is genetics. Just as neuropharmacology dominated schizophrenia research in the late twentieth century, genetics has been a leading focus in the first decade of this century.

• Although in the ‘genomic era’ such a shift was inevitable, it was also presaged by a generation of twin and family studies demonstrating high heritability. Reported concordance in monozygotic twins was roughly 50%, never the 100%, figure one might expect for a Mendelian disorder, but considerably higher than dizygotic twins or siblings.
18.3 LIFETIME RISKS OF DEVELOPING SCHIZOPHRENIA among relatives of an affected individual. Data are summarized from about 40 European family and twin studies conducted between 1920 and 1987. (After Gottesman, 1991; Prescott and Gottesman, 1993.)
Genetics

- Genetics of SCZ have been studied extensively. SCZ appears to be a relatively **highly polygenic disease with genetic variation** with frequencies from very common to rare (Kim, Zerwas, Trace, & Sullivan, 2011).

- High heritability has not, however, translated into a satisfying search for genetic lesions. Although early genome-wide or candidate-gene studies searching for common variants associated with schizophrenia were mostly disappointing, either because early findings failed to replicate or large-scale studies failed to detect genome-wide significance, recent international consortia combining single nucleotide polymorphism (SNP) data from several independent studies have found replicable associations with genes of the major histocompatibility complex (MHC) region on chromosome **6p21.3-22.1**, ZNF804A on chromosomes 2q32.1, neuregulin 1 (NRG1) on chromosome 8, as well as transcription factor 4 (TCF4) on 18q21.2.
Genetics

• Other studies have reported SNPs in candidate genes associated either with schizophrenia or a broad phenotype of psychosis, notably for genes within the neuregulin–ERBB4 signalling pathway, synaptic protein genes (for example, NRX1 (also known as PNO1)), a potassium channel (KCNH2) and many other brain-expressed proteins (for example, dysbindin).

• Currently, at least 43 candidate genes have been identified, but individual effect sizes are consistently modest, especially relative to the evidence for high heritability. Epistatic or additive effects of these variants may explain more of the risk, but results thus far on individual variants from case–control studies have not been useful for understanding an individual’s risk for schizophrenia.

• Hamshere et al., 2013: Genome-wide significant associations in schizophrenia to ITIH3/4, CACNA1C and SDCCAG8, and extensive replication of associations reported by The Schizophrenia Psychiatric Genome-Wide Association Study Consortium.
Genetics

- Disorder is believed to result from alterations during neural development that lead to improper function of synaptic transmission and plasticity, and in agreement, many of the susceptibility genes of SCZ encode proteins critical for neural development (Yin, Chen, Sathyamurthy, Xiong, & Mei, 2012).

- Recent review of eighteen genome-wide association studies of SCZ concluded that the most of the related genes of these studies are associated to neurodevelopment (including neuroplasticity, synapse maturation, neurogenesis), neuroendocrinology, and immunology (Hosak, Silhan, & Hosakova, 2012).
Genetics

• In addition to the many reports of common single nucleotide variations, many rare structural genomic variants, such as copy number variants and translocations, have been described in schizophrenia.

• These rare variants seem to have larger causative effects than previously reported SNPs, but most are not specific to schizophrenia and some occur only in a single family.

• The diversity and private nature of these mutations preclude a simple genetic explanation for schizophrenia, but these findings may yield important clues to pathophysiology.

• For instance, although the DISC1 translocation that confers very high risk for psychiatric disorder has been detected in only a single Scottish family, this private mutation has revealed important mechanisms of disease and identified a site where common variation may also confer risk.

• Even more encouraging, the consistent reports that so many of these structural variants affect genes implicated in brain development may predict the future of schizophrenia research.
Environmental factors

- Environmental factors identified so far have also implicated prenatal or perinatal events. Maternal malnutrition during famine, infections in the second trimester, perinatal injury and cytokine exposure have all been associated with subsequent increased risk for schizophrenia.
- Most of these effects are modest (less that two-fold increase in risk) and none seem specific for schizophrenia, but in aggregate they demonstrate that early adverse experiences, including mid-gestational insults, are a risk factor for psychosis occurring two decades later.
- Gene-by-environment studies may demonstrate more robust effects, but an even more promising approach may be epigenetic maps indicating the ‘scars’ of early experience or the stochastic changes emerging across development.
- As an example, a gene disrupted by a rare copy number variant in autism was found to be repressed by hyper-methylation in a large number of children with autism who had a perfectly normal genomic sequence.
What causes schizophrenia?

Schizophrenia remains unexplained. None of the abnormalities reported in the brains of schizophrenics is clearly diagnostic for the disease in the way that (say) plaques and tangles are for Alzheimer's disease. In the absence of a clear cellular pathology, the main clues as to the cause are epidemiological. There is general agreement that genes and environment are both involved; however, no genes have yet been identified, while most of the reported environmental influences are tentative hypotheses at best.

A recent paper, based on a very large cohort from Denmark, provides what may be the most comprehensive picture to date of the epidemiology of schizophrenia. The authors took advantage of the excellent civil registry and health care records in that country to analyze data from 1.75 million people, of whom 2669 developed schizophrenia; this sample included virtually every new case of schizophrenia between 1970 and 1993. The aim was to test the relative importance of some of the previously proposed risk factors in a large population.

The data confirm the well-known tendency for schizophrenia to run in families; individuals with a schizophrenic parent or sibling were almost ten times more likely to develop schizophrenia themselves, and for those with two affected parents the increase in risk was almost fifty-fold. The data also confirm a previously reported and puzzling season-of-birth effect; people born in March had a 10% elevated risk, whereas those born in September showed a correspondingly reduced risk. Perhaps most surprising is the effect of place of birth. Those born in the capital city, Copenhagen, had a 2.4-fold elevated risk compared to those born in rural areas, with intermediate risk factors for suburbs and provincial towns. (The risk was higher still for those born in Greenland—which belongs to Denmark—or in other countries, although sample sizes for those categories were relatively small.)

The implications become apparent when the numbers are translated into population attributable risk (PAR), which takes into account the number of people exposed to each risk factor. The factor with the greatest impact is place of birth, which the authors estimate accounts for 34.6% of the total PAR; the combined effect of place of birth and season accounts for 41.4%. Taking these numbers at face value, if the environmental risk factor(s) could be identified and eliminated, 41.4% of cases of schizophrenia could be prevented. Given that schizophrenia is estimated to affect about 1% of the world's population, the potential implications are dramatic indeed.

Clearly these findings will require careful scrutiny. One concern with any registry-based study is the accuracy of the diagnosis, but Denmark has good psychiatric services, and most of the experts we consulted felt that diagnostic errors were unlikely to undermine the conclusions. A more serious concern arises from the distinction between risk attributable to family history and risk attributable to genotype as a whole. The authors conclude that family history accounts for only 5.5% of the total cases, far less than the 41% attributed to environmental factors. Yet the contribution of genotype as a whole may be much greater than the family history would suggest.

Kenneth Kendler (Virginia Commonwealth University), who describes the data as "excellent", feels that the interpretation is flawed, because most people with a genetic vulnerability will not have an affected first-degree relative. Thus, although the authors may be technically correct in attributing only 5.5% of cases to the effect of parents and siblings, this is likely to substantially underestimate the importance of genetic effects. Bernard Devlin (University of Pittsburgh) agrees, and believes that the method used by the authors may also lead to an overestimate of the contribution of the environment.

It is difficult to guess by how much, he says, but it would clearly be premature to conclude that any one environmental risk factor accounts for more cases than does genotype.

Nevertheless, the environmental effects are substantial and seem to demand explanation. One possibility is exposure to infection, whether in utero or in early childhood; this would fit well with the effects of season and urbanization, and might also explain the effect of being born abroad, if for instance the mother is exposed to foreign pathogens to which she has less immunity. The evidence for the infection hypothesis, however, is still weak, according to Daniel Weinberger (National Institute of Mental Health), who believes that genetic explanations remain equally plausible; for instance, alleles that confer risk of schizophrenia on the offspring might also affect the behavior of their parents, making them more likely to migrate to cities, or more likely to mate in summer than in winter.

Further progress is likely to depend on the identification of susceptibility genes, which—given the promising signs from linkage studies—cannot be far away. It would be naive, however, to expect an early explanation of the disease, particularly given that even between monozygotic twins, concordance is only about 50%. Cloned genes might provide immediate insights (if, say, their expression is restricted to developing dopamine neurons), but this would be a stroke of luck indeed. Recall that the genes that cause familial Alzheimer's disease or Huntington's disease are ubiquitously expressed and have not yet led to a clear understanding of either disease process, despite a well-defined cellular pathology. The absence of such signs in schizophrenia may also be a problem in making animal models; how will we recognize a schizophrenic mouse?

The immediate impact of cloned genes will be on epidemiology, specifically on the ability to stratify the patient population by genotype to reveal environmental effects. Epidemiology in turn will provide important clues in the search for a cellular pathology; if, for instance, the effects of season and place of birth that are apparent in the Danish cohort really do signify a prenatal environmental influence, this should motivate an intensive study of brain development, and of the role of susceptibility genes, during the epidemiologically defined critical period.

Mapping the pathophysiology of schizophrenia

• These current unsatisfactory outcomes may change as we approach schizophrenia as a neurodevelopmental disorder with psychosis as a late, potentially preventable stage of the illness.
• This ‘rethinking’ of schizophrenia as a neurodevelopmental disorder, which is profoundly different from the way we have seen this illness for the past century, yields new hope for prevention and cure over the next two decades.
• A starting point for mapping the pathophysiology of schizophrenia can begin with the increasing recognition that this is a neurodevelopmental disorder, or perhaps more accurately a collection of neurodevelopmental disorders that involve alterations in brain circuits. Although Feinberg, Weinberger and Murray proposed this approach more than two decades ago, the field is only now providing the evidence and recognizing the implications of shifting to a neurodevelopmental approach.
Schizophrenia as a neurodevelopmental disorder

• Minor physical anomalies
• Premorbid neuropsychological and social deficits
• Obstetrical complications
• Exposure to adverse intrauterine events
• Morphometric abnormalities (lack of gliosis)
• Cytoarchitectural abnormalities
Some of the Schizophrenia Environmental Risk Factors

Cannabis use, the strongest known environmental risk factor for schizophrenia identified thus far, worsens gray matter brain volume loss in schizophrenia.
Grey-matter volume changes during normal development

Stage I: risk < 12 years
Stage II: prodome 12–18 years
Stage III: psychosis 18–24 years
Stage IV: chronic disability >24 years

Prefrontal excitatory synapses
Deficient myelination
Reduced interneuron activity
Excessive excitatory pruning

Myelination
Density of synapses

Newborn  6 years  14 years

$10^{15}$

Lateralization of brain
Cycles of myelination in the CNS during development.
Prominent anatomical abnormalities in the brain occur in some cases of schizophrenia.
The season of birth

• is related to the incidence of schizophrenia. More people with schizophrenia are born during cold weather months (i.e., January - April in the northern hemisphere and July - September in the southern hemisphere). One possible explanation for this finding is viral infection of the mother during pregnancy, since such infections occur seasonally.
Short Report

SEASON OF BIRTH AND CHESS EXPERTISE

FERNAND GOBET AND PHILIPPE CHASSY

Centre for the Study of Expertise, Centre for Cognition and NeuroImaging,
Brunel University, UK

Summary. The origin of talent and expertise is currently the subject of intense
debate, with explanations ranging from purely biological to purely environ-
mental. This report shows that the population of expert chess players in the
northern hemisphere shows a seasonal pattern, with an excess of births in late
winter and early spring. This effect remains when taking into account the
distribution of births in the population at large, using statistics from the
European Union member countries. A similar pattern has been found with
schizophrenia, and the possible link between these two phenomena is
discussed.
Fig. 1. Percentage of monthly births for (a) the EU population \(n=104,834,388\), from 1973 to 2001, except for 1975 and 1980. Source: Eurostat New Cronos database) and (b) EU chess players rated higher than 2000 points in the International Rating List \(n=24,923\). Source: World Chess Federation). The y-axis on the right depicts the percentage difference chess players minus population.
Genetics and development

• As a final link to development, the genetics of schizophrenia overlaps with the genetics of autism and other neurodevelopmental disorders.

• It is unclear why the same genetic variation associated with many different neurodevelopmental syndromes is manifested in some by age 3 years (autism) and in others after age 18 years (schizophrenia).
# The stages of schizophrenia (Insel, 2010)

## Table 1 | Stages of schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Features</strong></td>
<td>Genetic vulnerability</td>
<td>Cognitive, behavioural and social deficits</td>
<td>Abnormal thought and behaviour</td>
<td>Loss of function</td>
</tr>
<tr>
<td></td>
<td>Environmental exposure</td>
<td>Help-seeking</td>
<td>Relapsing–remitting course</td>
<td>Medical complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Incarceration</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Genetic sequence</td>
<td>SIPS</td>
<td>Clinical interview</td>
<td>Clinical interview</td>
</tr>
<tr>
<td></td>
<td>Family history</td>
<td>Cognitive assessment</td>
<td>Loss of insight</td>
<td>Loss of function</td>
</tr>
<tr>
<td></td>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disability</strong></td>
<td>None/mild cognitive deficit</td>
<td>Change in school and social function</td>
<td>Acute loss of function</td>
<td>Chronic disability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acute family distress</td>
<td>Unemployment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Homelessness</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Unknown</td>
<td>Cognitive training?</td>
<td>Medication</td>
<td>Medication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polyunsaturated fatty acids?</td>
<td>Psychosocial interventions</td>
<td>Psychosocial interventions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family support?</td>
<td>Rehabilitation services</td>
<td>Rehabilitation services</td>
</tr>
</tbody>
</table>

*Stage I, pre-symptomatic risk; stage II, pre-psychotic prodrome; stage III, acute psychosis; stage IV, chronic illness.*
Louis Wain (5 August 1860 – 4 July 1939) was an English artist best known for his drawings, which consistently featured anthropomorphised large-eyed cats and kittens.
Stage IV of schizophrenia involves chronic disability.

- In 1988, in the height of the AIDS epidemic, the editor of Nature noted that “schizophrenia is arguably the worst disease affecting mankind, even AIDS not excepted.”
- Not all individuals progress to this late stage of the illness, but for those who do the disability is not only psychiatric but medical. The oft-cited psychiatric deficits lead to unemployment, homelessness and incarceration, as noted earlier.
- A Finnish birth cohort study recently reported a 7% rate of suicide in schizophrenia, accounting for 50% of all deaths by age 39.
- The medical complications of chronic schizophrenia are less well known. In 2010, smoking and obesity are epidemic among people with schizophrenia, with estimates of nicotine dependence ranging from 58–90% and metabolic syndrome (obesity, hyperlipidemia, hyperglycemia and hypertension) present in 40%.
- Life expectancy for those with serious mental illness has been estimated at 56 years, approximately 25 years of premature mortality resulting usually from cardiopulmonary disease or other chronic medical conditions.
- Importantly, many of the medical complications of schizophrenia can be prevented through tobacco cessation, dietary management and programs to manage cardiovascular health.
Translational research for schizophrenia

- The accumulating genomic evidence indicates that there may be scores or hundreds of lesions contributing to this final common syndrome. The clinical evidence supports the possibility that what we have labelled schizophrenia for the past century may be many different disorders with different outcomes.

- And the stigma associated with the diagnosis, and the past history of misunderstanding and mistreatment also indicate that a change in the term may be advisable. In 2002, the Japanese terms for schizophrenia ‘Seishin-Bunreatsu-Byo’ (‘mind-split disease’) was replaced officially by ‘Togo-Shitcho-Sho’ (‘integration disorder’). Some evidence indicates that this name change led to reduced stigma, in that fewer people associated the new name with criminality.
Translational research for schizophrenia

• In the next decade the translational challenge will be to integrate the impact of genetics, experience and development to identify a complete blueprint of the risk architecture of this syndrome.

• This should lead to a new taxonomy, identifying the many disorders within the syndrome we now call ‘schizophrenia’ and hopefully replacing this aggregate label with a series of more precise diagnoses based on pathophysiology.

• There is a need for personalized and pre-emptive approach, based on understanding and detecting individual risk and facilitated by safe and effective interventions for those in stages I and II of this disorder.

• Importantly, if recovery defined as a life in the community is our primary goal today, for next decades our goals must include prevention, pre-emption and cure.
Translational approach for schizophrenia (Insel, 2010)

- Prevention
- Reducing the cognitive deficits
- Integration of care
- Stigma

Diagram:
- Discovery technologies:
  - Cognitive science
  - Developmental neuroimaging
  - Stem-cell biology
  - Clinical genomics/proteomics
- Pathophysiology:
  - Biodiagnostics for early detection
  - Treatment of cognitive deficits
- Translating research into practice:
  - Access
  - Integration
  - Social inclusion
- Strategic prevention
- Cure therapeutics
- Personalized care
- Diagnosis by late symptoms
- Treatment for psychotic episode

Stigma
Figure 2. Absolute mass, numbers of neurones, and numbers of nonneuronal cells in the entire adult human brain. Values are mean ± SD and refer to the two hemispheres together. B, billion.