"The intention [of this project] is to furnish a psychology that shall be a natural science."

By "natural science," Freud meant disciplines like biology and physics that deal with matter by using measurement and experimentation.
Curing mental illness with antibiotics

Paul Ehrlich 1854 - 1915

Treponema pallidum
Intellectual disability
Epilepsy
Bipolar affective disorder
Depressive episodes
Manic episodes
Young adult onset
ADHD
Inattention
Hyperactivity
Impulsivity
Early childhood onset
Schizophrenia
Delusions
Hallucinations
Cognitive deficits
Young adult onset
Autism
Impairment in social interaction
Impairment in speech and communication
Repetitive behaviours
Early Childhood onset
Enormous costs of mental health problems in Europe not matched by health services or research investment.

HEAVY BURDEN
Six categories of illness account for more than half of the costs of brain disorders in Europe. Indirect costs — such as working time lost to illness — are responsible for about 40% of the total financial burden.

TOTAL COST (2010)
€797.7 BILLION

*Other* includes brain tumour, child/adolescent disorders, eating disorders, epilepsy, mental retardation, multiple sclerosis, neuromuscular disorders, Parkinson’s disease, personality disorders, sleep disorders, somatoform disorder, stroke, traumatic brain injury.
Schizophrenia

- A chronic debilitating mental illness
- ~1% lifetime risk
- Characterised by delusions and hallucinations (positive symptoms)
- Amotivation, Alogia and Social withdrawal (negative symptoms)
- Devastating for the individual, the family and for society
- Ranked by WHO as 3rd most disabling illness in 18-44 age group, ahead of paraplegia and blindness
- Highly significant morbidity (~20% in full time employment)
- Significant mortality (life expectancy reduced by ~15 years)
Schizophrenia and related disorders are relatively common.
Schizophrenia: A neurodevelopmental disorder

People who later develop schizophrenia are more likely to:

- Be born in late winter or early spring
- To have had obstetric complications
- To be lighter at birth
- To have minor physical abnormalities
- To have impairments in motor, social and cognitive development
- To have a child psychiatric disorder
Schizophrenia-like disorders associated with organic disorders

- Associated with multiple genetic brain disorders including Epilepsy, Parkinsonism, Wilson’s disease, Huntington’s chorea, Friedreich’s ataxia, motor neuron disease.

- “These disorders have a range of symptoms similar to the general run of psychoses diagnosed as schizophrenia”

- “Organic cerebral cases should be rigorously excluded from any series of patients with “schizophrenia” being investigated…”

- “Brain disorders may be of particular importance in the psychoses with onset in childhood or in old age.”

Davison and Bagley, 1966
Autism

- Impairments in reciprocal social interaction
- Communication deficits
- Restrictive patterns of behaviour and interests
- Affects 1-2 per 1,000 (narrow definition) to 6 per 1000 (broad definition) males more than females
Review

Etiological heterogeneity in autism spectrum disorders: More than 100 genetic and genomic disorders and still counting

Catalina Betancur*
Genetic disorders associated with Autism symptoms

- Fragile X syndrome (FMR1)
- 15q11-q13 duplication syndrome
- Angelman syndrome (15q11 deletion; UBE3A)
- Prader-Willi syndrome (15q11 deletion)
- DiGeorge syndrome (22q11 deletion)
- 22q13 deletion syndrome
- 2q37 deletion syndrome
- PTEN hamartoma-tumor syndrome
- Tuberous sclerosis complex (TSC1, TSC2)
- Sotos syndrome (5q35 deletion; NSD1)
- Cornelia de Lange syndrome (NIPBL, SMC1A)
  - Down syndrome (trisomy 21)
  - Turner syndrome (45,X)
- Duchenne/Becker muscular dystrophy (DMD)
- Steinert myotonic dystrophy (DMPK)
- CHARGE syndrome (CHD7)
- Cohen syndrome (VPS13B)
- Creatine transporter deficiency (SLC6A8)
- Noonan syndrome (PTPN11)
- WAGR syndrome (11p13 deletion syndrome)

- Rett syndrome (MECP2)
- Neurofibromatosis 1 (NF1)
- Williams syndrome (15q11 deletion; UBE3A)
- 7q11.23 duplication syndrome
- Smith-Magenis syndrome (17p11.3 deletion; RAI1)
- Potocki-Lupski syndrome (17p11.3 duplication; RAI1)
- Smith-Lemli-Opitz syndrome (DHCR7)
- Rubinstein-Taybi syndrome (CBP)
- Timothy syndrome (CACNA1C)
- Cortical dysplasia-focal epilepsy syndrome (CNTNAP2)
- Joubert syndrome (10 genes)
- Kleefstra syndrome (9q34.3 deletion; EHMT1)
- Wolf-Hirschhorn syndrome (4p16.3 deletion)
- Rett-like syndrome with infantile spasms (CDKL5)
  - ARX-related syndromes
  - Adenylosuccinate lyase deficiency (ADSL)
  - Female-restricted epilepsy with MR (PCDH19)
- Alpha thalassemia/MR syndrome X-linked (ATRX)
  - Mitochondrial disorders (+++ genes)
  - Metabolic disorders (+++ genes)

All these genetic disorders are also well-known causes of mental retardation
Gene mutations in Schizophrenia and Autism

• Involved in the development/wiring of the brain

• Involved in the synapse - the point of connection between nerve cells

• Some mutations may cause either schizophrenia or autism

• Many gene mutations also involved in learning disability
How many mutations are there?

VIPR2 duplications
PAK7 dup
NRXN1 deletion
Chr 16p11.2
Chr 3q29 deletion
Chr 1q21.1
Chr 15q13 deletion
Chr 16p11 dup
C16orf72
Chr 22q11 deletion syndrome
DISC1

Estimated that 5% of schizophrenia patients carry one of these mutations…so far
Rett Syndrome

- Almost exclusively affects girls
- Loss of purposeful hand movements and language
- Delay in new motor skills and abnormal movements
- Autism like symptoms such as loss of social interaction
- Seizures

Causes of Rett Syndrome

- Most cases caused by a mutation in the methyl CpG binding protein 2, or MECP2 gene.
- The MeCP2 protein controls the expression of many other genes involved in function of the synapse

Rett syndrome in Mice

- Lose motor coordination at 5 weeks
- Show abnormal social behavior
- Learning and memory deteriorates.
- Repetitive behaviors emerge
- Repeatedly clasp their forepaws together

Treatment of Rett syndrome in Mice

- The effects of mutated MECP2 can be overcome by using growth factors
- IGF1 can be used to treat the symptoms in Mice
- Human trials of IGF1 are underway
**Fragile X Syndrome**

- Affects boys
- Learning disability
- Hyperactive and impulsive
- Delay in crawling, walking, or twisting
- Symptoms of autism
- Distinctive physical features

**Cause of Fragile X**

- Expansion of a portion of the FMR1 gene on the X chromosome
- Gene promoter is silenced leading to the absence of the protein
- Absence of protein causes increased synthesis of other proteins at the synapse

**Fragile X syndrome in Mice**

- Symptoms mimic the human condition

**Treatment of Fragile X in Mice and Humans**

- Activation of GABA-B with Arbaclofen corrected synaptic abnormalities in Mice
- Inhibition of mGLuR receptors improves symptoms in Mice
- Early promising signs of improvement in humans using Arbaclofen
Milestones in understanding the biological basis of Fragile X syndrome

- 1943: Martin-Bell syndrome described
- 1953: Watson & Crick publish structure of DNA
- 1969: Constriction on X chromosome identified in FXS
- 1977: Conditions identified to express "marker X" fragile site
- 1991: FMR1 gene identified
- 1993: FMRP protein described
- 1994: Fmr1 KO mouse model generated

- 1982: BCM theory of cortical plasticity proposes homosynaptic LTD
- 1986: "Metabotropic" action of glutamate described
- 1988: mGluRs discovered, hypothesized to trigger LTD
- 1991: Group 1 mGluR sequenced
- 1992: Homosynaptic LTD discovered
- 1997: mGluR stimulation induces FMRP synthesis at synapses
- 1998: mGluR-dependent protein synthesis prolongs epileptiform bursts
- 2000: Protein synthesis-dependent mGluR-LTD described
- 2002: mGluR-LTD exaggerated in Fmr1 KO mice
- 2005: MPEP ameliorates fragile X phenotypes in animal models
- 2007: Genetic reduction of mGluRS corrects multiple Fmr1 KO phenotypes in mice
- 2009: Clinical trials initiated using mGluRS inhibitors to treat FXS
Curing mental illness with antibiotics

Paul Ehrlich 1854 - 1915

Treponema pallidum
An autoimmune disorder affecting the Brain

Anti-NMDA receptor encephalitis with the initial presentation of psychotic mania
Yen Lin Kuo a,b, Hsing Fang Tsai a,b, Ming Chi Lai c, Chien Ho Lin f, Yen Kuang Yang a,b,c,d,*

Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis
Helen Barry, Orla Hardiman, Daniel G. Healy, Mary Keogan, Joan Moroney, Peter P. Molnar, David R. Cotter* and Kieran C. Murphy*

CASE REPORT
Open Access

Anti-N-methyl-D-aspartate receptor encephalitis presenting with acute psychosis in a preteenage girl: a case report
Anti-NMDA receptor encephalitis: an important differential diagnosis in schizophrenia

Symptoms
• Prodromal ‘viral’ phase
• Symptoms of schizophrenia or severe depression
• Seizures
• May become mute or catatonic

Diagnosis
• Detection of anti-DMDA antibodies in serum or CSF

Treatment
• Steroids
• Immunosuppressive agents
• Plasma exchange
The Promise of Molecular Medicine in Brain disorders

Krueger and Bear, 2011
Clinical implications for diagnosis and nosology

- There are multiple forms of schizophrenia and autism
Clinical implications - genetic testing

Chromosomal microarray offers a much higher diagnostic yield (15-20%) for genetic testing of individuals with unexplained developmental delay/intellectual disability, autism spectrum disorders or multiple congenital abnormalities than G-banded karyotype and is recommended as a first tier cytogenetic test.

International Standard Cytogenomic Array Consortium, 2010
Clinical implications - genetic counselling

- Without genetic testing an empirical recurrence risk for ASD in a sibling is ~5%
- If diagnosed as inherited highly penetrant mutation, then recurrence risks are more accurate (up to 50%)
- If de-novo, then risk might be no more than population risk
Clinical implications – early intervention

- Early intervention in Autism can result in significant improvements in IQ, language, adaptive behaviour and autism diagnosis
  Dawson et al, 2010

- Longer duration of untreated psychosis is related to poor outcome in schizophrenia
Clinical implications - treatments based on molecular subtype?

- Systemic treatment of MeCP2 mutant mice with IGF-1 extends life-span, improves motor function and increases brain weight
- Treatment of an adult male patient with 15q13 deletion (CHRNA7), schizophrenia, rage outbursts, and Epilepsy with galantamine a positive regulator of the α7nAChR (Cubells et al, 2011).
- Recognition and treatment of rare cases with known underlying biology eg. Anti-NMDA receptor encephalitis