KING'S College LONDON

INSTITUTE OF PSYCHIATRY,
PSYCHOLOGY & NEUROSCIENCE

Module:

Biological Foundations of Mental Health

Week 4:

Biological basis of learning, memory and cognition

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Topic 2:

From the dynamic synapse to synaptopathies

Part 4 of 4

Topic list

This week, we will be looking at the following topics:

- Topic 1: Learning, memory and synaptic plasticity
- ***Topic 2: From the dynamic synapse to synaptopathies***
- Topic 3: The effects of activity, experience and deprivation on the nervous system

Click **Next** to continue

Part 4

Features of schizophrenia

Schizophrenia is a chronic disease affecting approximately 1% of the population.

Positive symptoms:

- hallucinations
- delusions

Negative symptoms:

- blunted affect
- avolition
- asociability

Thought disorders:

- working memory deficits
- cognitive deficits

Heterogenous:

- symptoms may vary from patient to patient

Louis Wain's Cats, by Louis Wain (British Artist (1860-1939)): famous for painting cats; developed a mental illness later on in life, commonly believed to be schizophrenia. The progression of this illness could be seen in his paintings (controversial).

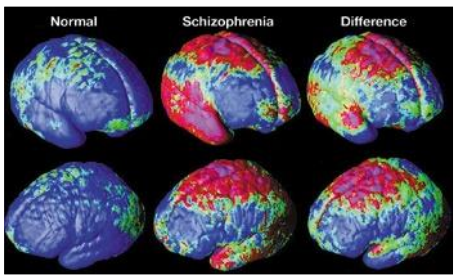
Current treatments

Antipsychotic drugs	Behavioural treatment
Haloperidol, olanzapine and clozapine	Cognitive behavioural therapy, adherence therapy
Good at addressing positive symptoms	Used as an adjunct to anti-psychotic drug treatment, effective in reducing relapse and resistant symptoms
A quarter of patients are non-responsive	Little impact on the negative and cognitive symptoms, therefore little impact on functional recovery
Little impact on negative symptoms and thought disorders or cognitive deficits	
Side effects include sedation, weight gain and motor deficits	

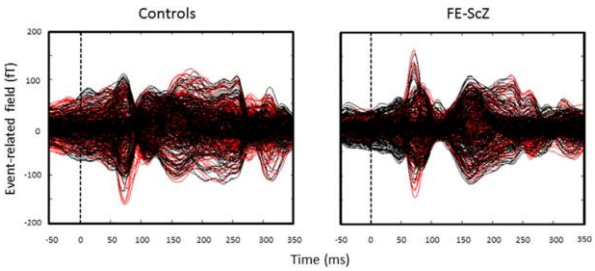
Pathology of schizophrenia

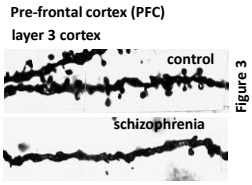
Reduced grey matter in patients when compared to unaffected individuals

Differences in overall **brain volume**



Dysfunction in neuronal network function in schizophrenic patients





Reduced number of dendritic spines in patients with schizophrenia

Glantz & Lewis, 2000; Rivolta et al. (2014); Thompson et al. (2001)

Genes and environment

Environmental factors:

Genetic susceptibility:

- Rare mutations: low occurrence, high penetrance eg NRXN1, 22q11.2 deletion, DISC1, NRXN1
- Common variants: high occurrence, low penetrance eg TCF4, ZNF804A

Altered gene expression → Altered brain wiring → Impaired information processing → Schizophrenic symptoms

The genetic landscape of schizophrenia is highly complex:

- some mutations are very rare but with a strong effect
- many variants have a weak effect, only slightly increasing chances of developing the disease

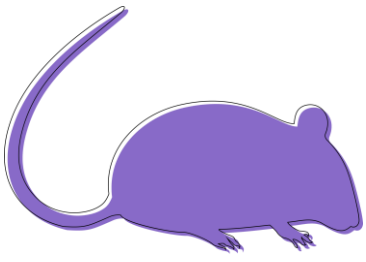
It is thought to be a combination of environmental factors and both rare and common genetic variants that underlie schizophrenia.

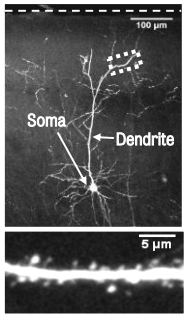
Sullivan et al (2012); Horváth & Mirnics (2009)

Modelling synaptic defects in schizophrenia (1)

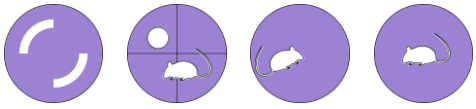
Animal models

Ability to look at overall morphology of the cell and examine how altering specific gene expressions can impact animal behaviour





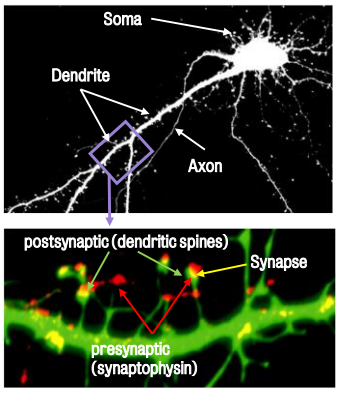
Behaviour



Primary neuronal cell cultures

An easy way to manipulate gene expression and allows us to examine dendritic spines in detail

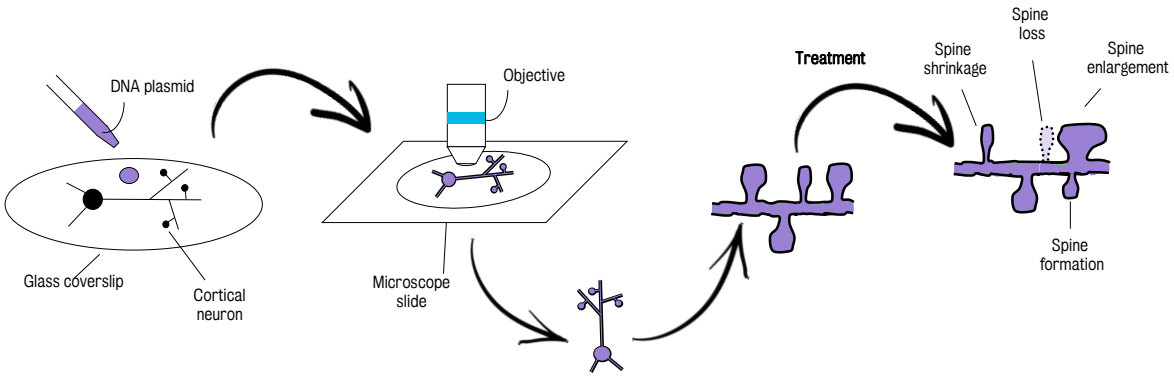
Cortical Pyramidal Neuron



Modelling synaptic defects in schizophrenia (2)

We can use neurons grown in a dish to examine or model synaptic deficits in schizophrenia.

Manipulate expression of target gene	Image neurons	Dendrite spine analysis



Modified from Srivastava et al., 2011

Modelling synaptic defects in schizophrenia (3)

Interacting proteins: PDE4, GSK3b, TNIK, Kal-7, PCM1, NDEL1, NDE1, LIS1

Cellular localisation

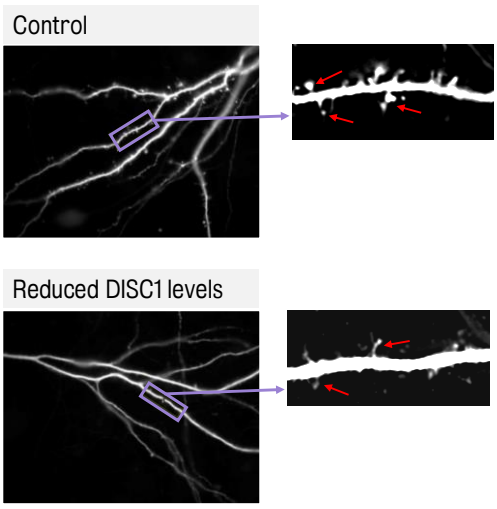
- Presynaptic density
- Postsynaptic density
- Centrosome
- Cytosol
- Nucleus
- Growth cone
- Mitochondria

Affected functions

- Grey matter volume
- White matter volume
- Synapse function
- Hippocampal function
- Working memory

Related disorders

- Schizophrenia
- Schizoaffective disorder
- Bipolar disorder
- Autism spectrum disorder
- Recurrent major depression



DISC1 plays a significant role in the maintenance of dendritic spines; therefore alterations in the expression level of the protein **could impact synaptic connectivity in the brain**.

Summary

- dendritic spines are important for how the brain wires together
- disturbances/alterations in neuronal and synaptic structure is associated with mental illnesses
- multiple lines of evidence indicate that neuronal wiring is altered in schizophrenia
- a number of the genetic factors associated with schizophrenia encode for proteins found at synapses
- we can model the effects of altering the expression of proteins in neurons grown in a dish

References

[1] Glantz, L. A. & Lewis, D. A. (2000). Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Archives of general psychiatry*, 57(1): 65-73.

[2] Horváth, S. & Mirnics, K. (2009) Breaking the gene barrier in schizophrenia. *Nature medicine*, 15(5): 488-490.

[3] Rivolti, D. Castellanos, N. P., Stawowsky, C., Helbling, S., Wibral, M., Grützner, C. & Singer, W. (2014). Source-reconstruction of event-related fields reveals hyperfunction and hypofunction of cortical circuits in antipsychotic-naive, first-episode schizophrenia patients during Mooney face processing. *Journal of Neuroscience*, 34(17): 5909-5917.

[4] Srivastava, D. P., Woolfrey, K. M. & Penzes, P. (2011). Analysis of dendritic spine morphology in cultured CNS neurons. *JoVE* (*Journal of Visualized Experiments*), (53): e2794.

[5] Sullivan, P. F., Daly, M. J. & O'Donovan, M. (2012). Genetic architectures of psychiatric disorders: the emerging picture and its limitations. *Nat Rev Genet*, 13(8): 537-51.

[6] Thompson, P. M., Vidal, C., Giedd, J. N., Gochman, P., Blumenthal, J., Nicolson, R. & Rapoport, J. L. (2001) Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proceedings of the *National Academy of Sciences*, 98(20): 11650-11655.

Additional reading

[1] Avino, T. A., & Hutsler, J. J. (2010). Abnormal cell patterning at the cortical gray–white matter boundary in autism spectrum disorders. Brain research. 1360: 138-146.

[2] Giagtzoglou, N., Ly, C. V., & Bellen, H. J. (2009). Cell adhesion, the backbone of the synapse:"vertebrate" and "invertebrate" perspectives. Cold Spring Harbor perspectives in biology, 1: a003079.

[3] Yuste, R., & Bonhoeffer, T. (2004). Genesis of dendritic spines: insights from ultrastructural and imaging studies. Nature Reviews Neuroscience, 5(1): 24.

End of topic