Lecture 7: Schizophrenia Spectrum Disorders

What is Schizophrenia?

- Think of ‘madness’ and many people think of schizophrenia.
- One thing it is **not** is ‘split personality’
- The confusion arises due to the meaning of the word itself ‘split mind,’ but in fact schizophrenia is not a disorder of personality at all.
- It is probably best described as a detachment from reality in which the sufferer experiences hallucinations, delusions and a possible host of other symptoms.

Psychosis or Neurosis?

- A neurosis refers to a disorder of affect or mood, such as anxiety, panic, phobias and depression. People suffering form neurotic disorders are treated with sympathy and understanding.

- Psychosis on the other hand is outside of most people's comprehension and refers to a detachment from reality. Symptoms may include hallucinations (auditory and visual) and delusions, thought disorders etc.

The symptoms

- The symptoms are so varied that it is useful to categorise them in one of a number of ways:
- Schneider (1959) described 'first rank symptoms.' Originally, to be diagnosed with schizophrenia one or more of these needs to be present:
- Thought disturbance
- Hallucinations
- Delusions

Diagnosis under DSM-IV

- To be diagnosed under DSM-IV, an individual must be suffering from one or more of the following symptoms:
- Control of thoughts.
- Hallucinatory voices.
- Delusions of control.
- Other persistent delusions.

However- more recently;

- The symptoms of schizophrenia are not constantly present.
  - Vary at different times of day
  - Some individuals may have “triggers”
- Different individuals with schizophrenia may show very different symptoms.
- Hughlings Jackson described two categories of symptoms: positive and negative.

This is a particularly useful way in which symptoms can be viewed:

- **Positive symptoms:**
- These refer to the characteristics that appear in addition to existing behaviours, for example hallucinations, delusions and thought disturbances such as thought insertion.
- **Negative symptoms:**
- Refers to those symptoms that an impairment of usual behaviours such as psychomotor disturbances, lack of volition, disturbances of mood and thought disorders.

- ***This is useful since it appears that the dopamine hypothesis (medical model) accounts for positive symptoms whereas other explanations (serotonin or brain structure) are implicated when explaining negative symptoms.***

Under DSM-IV there were several `types`

- **Paranoid schizophrenia**
- **Disorganised schizophrenia (formerly hebephrenic)**
- **Catatonic schizophrenia**
- **Simple schizophrenia**

Mike

Mike is a 33 year old divorced male with two children he rarely ever sees, ages 8 and 10. He has never been seen by a psychiatrist. His family doctor has tried to get him to see a local psychiatrist but Mike refuses to go. Mike says he knows someone has removed his brain and replaced it with someone else's. He believes that this brain is controlling him and that he is not responsible for his actions. He works everyday and has been in his current job for 15 years. He says he has lots of friends but sometimes he thinks its one of them who did this to him. He is convinced that he must protect his brain by wearing a hat (even to bed).

His speech is fine and Mike goes to work everyday. He doesn't think his thoughts are unusual.

Tommy

- Tommy is 41. According to family he has always been withdrawn and at times his behaviour is inappropriate. His sister-in-law gave the example of him waking her up in the middle of the night to cook breakfast!
- Over the last year Tommy frequently talks at length and is difficult to understand. He often goes days without speaking to people.

Mary

- Mary is 21 and was first presented to the psychiatric services as an out-patient at the age of 19. She gave a two month history of social withdrawal associated with paranoid delusions. A diagnosis of probable paranoid schizophrenia was made and she was treated accordingly.
- However, her condition continued to deteriorate. Over the next two months she became withdrawn and mute, and was admitted to hospital. At this time she began to have episodes of freezing and started to walk backwards. During her freezing episodes she should stand rigid for hours and ignored any instructions from nurses to move.

However, with DSM-5 things have changed…

- DSm-5 has moved away from a single disorder with separate sub-types and now has five separate psychotic disorders ranging across the spectrum depending on their **severity, duration and complexity**.
- The categories are:
  - Schizophrenia
  - Schizotypal Personality Disorder (covered in the P.D. lecture)
  - Delusional Disorder
  - Brief Psychotic Disorder
  - Schizoaffective Disorder

DSM-5: Key features

- The diagnosis of schizophrenia has expanded in DSM-5. **Criterion A** now includes five items:
- 1. Delusions.
- 2. Hallucinations.
- 3. Disorganized speech (e.g., frequent derailment or incoherence).
- 4. Grossly disorganized or catatonic behaviour.
- 5. Negative symptoms (i.e., diminished emotional expression or avolition)
- At least two of the five symptoms must be present for at least one month. One of the two symptoms must be delusions, hallucinations, or disorganized speech.
- Negative symptoms, which impair function the most, are now officially recognised.

- **Criterion B** for schizophrenia gets more attention in DSM-5: “Level of functioning… is markedly below the level achieved prior to the onset”.
- *This is not a criterion for schizoaffective disorder. (This is unchanged from DSM IV).*
- The previous specifiers for schizophrenia (paranoid, disorganized, catatonic, etc.) have disappeared; now, specifiers are related to the illness course (“first episode” versus “multiple episodes”; state of remission; etc.).
- “Currently in full remission” is a specifier. People can and do get better from schizophrenia. (DSM states that 20% of people with schizophrenia have a “favourable course”.)
- The authors explicitly comment about “decrements” in cognitive function in people with schizophrenia, which frames the condition as a brain disease. Similarly, there’s a note that “unawareness of [schizophrenia in the patient] is typically a symptom of schizophrenia itself rather than a coping strategy.”

Catatonic specifiers and new Catatonic Disorders:

- The catatonic subtype has been eliminated. However, a catatonic specifier has been added and may be used with depressive, bipolar, and psychotic disorders.
- This recognizes that catatonia occurs across several categories of disorders, without necessarily indicating psychosis.
- In addition, there are two new catatonic disorders: Catatonic Disorder due to Another Medical Condition and Other Specified Catatonic Disorder.

Key Cognitive and behavioural features for differential diagnosis

- **Delusions (positive):**
  - Firmly held erroneous beliefs or misinterpretations of perceptions or experiences.
  - Fixed and unchangeable beliefs.

  Frith (1996) proposes that these stem from an inability to integrate perceptual input with prior knowledge.

  Morrison (2001) argues that they stem from biased information processing and dysfunctional beliefs about the world, individuals jump to conclusions based on minimal information.

  Types of delusions range from persecutory, grandiose, delusions of control, delusion of reference, nihilistic delusions and erotomanic delusions.

Key Cognitive and behavioural features for differential diagnosis

- **Hallucinations (positive):**
- Sensory abnormalities across a range of modalities; auditory, tactile, gustatory, olfactory and visual in 70% of sufferers.
- Auditory hallucination is reported the most, with sufferers hearing voices commanding that they act, or `hearing a conversation` (although we know that it is from an internal source). Visual comes next, followed by tactile and somatic.
- Some sufferers believe them to be true, whereas others recognise that they are not. They appear to stem from a `reality monitoring` and/or `self monitoring` deficit.

Key Cognitive and behavioural features for differential diagnosis

- **Disordered thoughts/speech (positive):**
- Derailment- drifting from one topic to the next.
- Loose associations- drifting from one conversation to another.
- Tangenital speech- irrelevant answers.
- Clanging- thoughts driven by word sounds.
- Neologisms- made up words.
- Word salads- no links between words at all.

Key Cognitive and behavioural features for differential diagnosis

- **Disordered motor behaviour (positive):**
- Inappropriate behaviour for chronological age.
- Or agitated behaviour.
- Inappropriate behaviour for the context.
- Inappropriate clothing or hygiene.
- Catatonic motor behaviours.

Key Cognitive and behavioural features for differential diagnosis

- **Negative symptoms:**
- Common for schizophrenia, but less so for the other psychoses.
- Diminished emotional expression (affective flattening).
- Avolition (lack of goal orientated behaviour).
- Alogia (lack of verbal fluency).
- Asociality (social withdrawal).

Diagnosis of the Schizophrenic Spectrum Disorders

- **Delusional Disorder**:
- One or more delusions last at least one month
- Normal functioning is not markedly impaired and behaviour is not bizarre
- Any manic or major depressive episodes which have occurred have been brief in relation to the delusional episode
- The disorder is not directly attributable to substance/medication use or any other mental disorder

Diagnosis of the Schizophrenic Spectrum Disorders

- **Brief Psychotic Disorder**:
- Presence of at least one of the following-
  - Delusions, hallucinations, disordered speech or disorganised behaviour.
- The disturbance last between 1 day and1 month and behaviour returns to normal
- The disorder is not attributable to substance/medication use or other mental disorder

Diagnosis of the Schizophrenic Spectrum Disorders

- **Schizophrenia**:
- At least two of the following present for a significant period of time in one month:
  - Delusions, hallucinations, disorganised speech, disorganised behaviour, negative symptoms
- The ability to function in one or more major areas (work, self care etc.).
- Continuous signs of the disorder for at least 6 months.
- The disorder is not directly attributable to substance/medication use or any other mental disorder

Diagnosis of the Schizophrenic Spectrum Disorders

- **Schizoaffective Disorder**:
- A continuous period of illness during which there is a major mood episode
- Delusions or hallucinations for 2 or more weeks without a major mood episode
- Symptoms for a major mood episode are present for the majority of the illness
- The disorder is not directly attributable to substance/medication use or any other mental disorder

Onset and Development

- Onset of schizophrenia occurs in the late teens or early twenties:
  - Neurodevelopmental hypothesis
- Some individuals with schizophrenia display the symptoms throughout their life.
  - A subgroup of individuals who, a few years after the initial display of symptoms, show a lack of symptoms even without treatment (see Jobe & Harrow, 2010 for an overview).
  - Even with symptoms, some individuals are able to be part of the social and economic world experienced by healthy individuals.

Onset and development

- Neural changes during adolescence can influence development of schizophrenia.
- Environmental factors may also play a role:
  - Early life adversity.
  - Growing up in an urban environment.
  - Cannabis use.

Prevalence

- Lifetime between 0.3 and 1% (VanOs & Kapur, 2009).
- On average sufferers die 10 years earlier than non sufferers.
- 10% die from suicide.
- Sufferers` mortality rates are 50% higher than rest of the population.
- 80% continue to experience problems with social functioning.
- 79% never work at all.
- The prevalence is similar across the world, but less severe in developing countries… why? (WHO).

Prevalence

- Cultural differences? In a UK study by King et al. (2005), the reporting of psychotic symptoms is higher in ethnic minority groups than for ethnic white groups.
- The incidence of reporting for African Caribbean populations was twice as high than whites.is this a reflection of racial disparities in mental health treatment?
- In `within` country studies, the prevalence is higher for immigrants than for indigenous populations.
- Gender differences? Similar rates, but females diagnosed later and less likely to require hospitalization, have better social functioning and a better outcome.

The course of psychotic symptoms

- **1. The Prodromal Stage:**
- Usually late adolescence/early adulthood.
- 51% develop between ages of 15 and 25.
- 80% develop symptoms between 15 and 35.
- Whilst the development is rapid for some, for most it is a gradual deterioration over approximately 5 years, characterized by withdrawal, inappropriate emotions and a deterioration on personal care.
- Studies show grey matter loss (Bhojraj et al., 2011).
- Why this age? Diathesis stress?
- 70% of people who develop the symptoms experience stressful life event in the previous 3 weeks (Harrop & Trower, 2001).

The course of psychotic symptoms

- **2. The Active Stage:**
- Ambiguous symptoms manifesting as hallucinations, delusions, disordered motor behavior and speech.
- **3. Residual Stage:**
- Recovery is gradual, with some symptoms remaining. This stage is where positive and negative symptoms cease.
- Long-term studies show that- 28% of sufferers remit after one active stage, 22% continue to show symptoms, 50% alternate between active and residual stages and only 40/50% adhering to treatment.

Aetiologies: Biological

- The incidence of schizophrenia in the general population is around 1%.
- Anything higher is deemed to have a potential genetic contribution.
- **As with all of the other behaviours we have explored, it is vital to bare in mind that it is very difficult to separate out the effects of genetics and the environment, even when monozygotic twins are reared apart.**

Twin studies

- **Gottesman & Shields (1972)** 57 schizophrenic twins between 1948 and 1964.
  - About 40% of the twins were determined to be MZ and about 60% DZ.
- Concordance rates were as follows:
  - Monozygotic twins 42%.
  - Dizygotic twins 9%.
- **Gottesman (1991)** in a review of over 40 other studies found-
  - Monozygotic twins 48% concordance.
  - Dizygotic twins 17%.

- **Heston (1970)** found that if one MZ twin has schizophrenia that there's a 90% probability that the other will have 'some sort' of mental disorder!
  - But, not necessarily SCHZ.

- **What this suggests:**
  - **There is a genetic link for schizophrenia?**
  - **Schizophrenia is not entirely genetic, otherwise the concordance for MZ twins would be 100%.**

- However, it is vital to consider the role of environmental factors.
- MZ twins are more likely to be brought up in similar conditions, be treated similarly, same class at school, have similar friends and experiences, even be dressed and treated similarly.
  - Therefore high concordance is not surprising.
- A way around this is considering MZ twins reared apart.
  - However, as Gottesman (1991) discovered the concordance rates are similarly high.
  - But, the same proviso still applies. Twins that are adopted into different families still tend to be reared similarly and are often adopted into members of the same family! (Kamin 1977).

- One other point - until the advent of sophisticated genetic testing it was difficult to distinguish MZ and DZ twins, especially at birth.
- Therefore, some of the statistics for MZ twins may actually be for DZ twins and vice versa.
- And we tend to assume that MZ twins are treated more alike because they are MZ twins.
- Lytton (1977) turned this on its head and suggested that the greater similarity of MZ twins ensures that they elicit a more similar response from their parents.

Family studies

- Family studies examine the possibility of getting the disorder if parents have the disorder. If this is greater than 1% then this could be seen as possible support for the genetic cause.
- However, the same proviso`s remain. Living with a schizophrenia sufferer could increase your chances of developing it yourself….
- How?

Gottesman (1991) reviewed other studies:

Circumstances	Probability of developing schizophrenia
‘Randomly’ chosen from population	1%
Brother or sister has schizophrenia	8%
One parent has schizophrenia	16%
Both parents have schizophrenia	46%

Perhaps the most powerful of all evidence for a genetic link is the following:

- **Gottesman & Bertelsen (1989).** If your parent is an identical twin who has schizophrenia then you have a 17% chance of getting it too.
- However, if your parent does not have the disorder, but their identical twin does, then your chance of getting the disorder is still 17%.
- Good evidence?
- It seems to minimise environmental causes since you are not living with a schizophrenia sufferer.
- However, you are living with someone who is predisposed to schizophrenia, since they have the same genetic code as their twin who has developed it.

Adoption studies

- Kety et al. (1978) looked at adopted children in Finland who had developed the disorder.
- **Findings**: Their biological parents were more likely to have schizophrenia than the parents who had adopted them and brought them up.
- Heston (1947) followed 47 children born to schizophrenic mothers but who were separated within the first three days of life.
- They were adopted into families not related to the biological mothers. Later in life (30`s) they were compared to a control group of children who had been separated in similar circumstances at birth, but crucially, not born to schizophrenic mothers.
- Five of the 47 in the experimental group had gone on to develop schizophrenia (over 10%), whereas none of those in the control group had developed the disorder!

Adoption studies and more…

- Wahlberg et al. (2004) found that genetic factors were important predictors of schizophrenia IF there were similar environmental factors in the home environment.
- Recent genetic studies show that there is a general overlap between schizophrenia and other schizophrenia spectrum disorders.
- May this be representative of a set of genes which affect differential diagnosis?
- Recent evidence of poor performance on an eye-tracking task suggests this is a marker for the inheritance of schizophrenia.
- 30-45% of first degree relatives have poor performance on these tasks (regardless of diagnosis) and in MZ twins even in the absence of schizophrenia the concordance rates are still high (Trillenberg et al., 2004).

Conclusions

- Genes appear to play a role although other factors must also be involved.
- The chromosome or specific gene(s) responsible have not yet been identified.
- The tips of chromosomes 5 and 22 were suggested as possible sites for the faulty genes but are now discounted.
- More recently- the COMT gene on chromosome 22, responsible for producing enzyme that breaks down dopamine (referred to as the Val allele).
- Individuals with the Val allele have small but consistent increased risk of SCHZ and impaired PFC performance (Prata et al., 2009).

Biochemical causes

- Anecdotal evidence:
- Some hallucinogenic drugs such as LSD produce symptoms that are indistinguishable from schizophrenia.
- Cocaine and amphetamines can produce hallucinations and delusions of persecution, again not dissimilar to those reported by schizophrenia sufferers.
- Smythies (1976) found traces of hallucinogenic chemicals in the CSF of schizophrenia sufferers. One role of the CSF is to mop up excess chemicals in the brain. These findings suggest that schizophrenics are producing more of these chemicals than `normals`.

The Dopamine Hypothesis

- Hallucinogenic drugs are chemically similar to the neurotransmitter dopamine, therefore dopamine could be the cause.
- Researchers concluded that the brains of schizophrenics were more sensitive to dopamine than the brains of non-schizophrenics.
- L-Dopa (a chemical that increases the levels of dopamine) can produce schizophrenic symptoms.
- Chlorpromazine, (anti-psychotic), blocks dopamine receptor sites. This makes the brain less sensitive to dopamine.
- Post mortems carried out on schizophrenia sufferers, show that they have up to six times more dopamine receptors than normal. This suggests that their brains are more sensitive than usual to the neurotransmitter.

And…

- Brain imaging shows excessive levels of dopamine released from the basal ganglia (Carlsson, 2001).
- Seeman & Kapur, (2001) reported an increase in D2 receptors in the limbic areas post mortem.
- Both the mesolimbic and mesocortical pathways have different effects on psychotic symptoms.
- The effects of D2 excess is limited to the mesolimbic pathway; drugs help these positive symptoms. However the mesocortical pathway relates to the negative symptoms and the PFC; here the levels of dopamine are decreased, where the neurons **may be** underactive in dopamine production…

But…

- Chlorpromazine (typical antipsychotic) only reduces the positive symptoms of schizophrenia (mesolimbic pathway).
- Neuroleptic drugs have their effect on the brain almost immediately, but they take weeks to affect the behaviour of the patients. The dopamine hypothesis is unable to explain this delay.
- Chlorpromazine makes little or no difference to 30% of schizophrenic sufferers.
- Recent evidence suggests that the PFC deficits are not a result of less neurons, but to disrupted connections in GABA and D2 pathways (Seshadri et al., 2013).

The role of serotonin

- Kane (1988) clozapine (newer atypical) has been used in treatment. Clozapine is more effective in reducing the negative symptoms of schizophrenia. Clozapine seems to work by blocking serotonin sites in the brain.
- **Conclusion**
- Barlow & Durand (1995): both dopamine and serotonin are probably involved, but the precise role played by each is unclear.
- ***All the evidence provided is correlational. It implies an association between schizophrenia and chemicals in the brain. It could be that schizophrenia has caused the abnormal chemical levels rather than the other way around.***
- However the presence of enlarged ventricles are observed prior to first episode.

Clozapine, serotonin and GABA

- The newer atypical antipsychotics produce a strong blockage of serotonin and only a weak blockage of D2 receptors.
- Downar & Kapur, (2008) suggest a complex interaction between serotonin and dopamine pathways.
- GABA and glutamate are the 2 principal NT`s within the cortex (Wassef et al., 2003).
- Glutamate excites and GABA inhibits the pathways associated with the PFC, limbic system and temporal structures.

Neuro-developmental

- Johnson (1989) some sufferers have a reduced blink reflex, evidence for neurological damage.
- Others have reported that some have difficult births possibly starving the brains of oxygen. This could explain why the incidence of schizophrenia is declining as birth techniques improve.
- Chua & Mckenna (1995) reported the following abnormalities in the brains of some schizophrenics:
- Smaller corpus collosum.
- Less grey matter (synapses) in the temporal lobes.
- Enlarged ventricles resulting in loss of brain tissue.
- Reduced activity in the prefrontal cortex.

Neural changes

- Individuals with schizophrenia have different activity in the dorsolateral prefrontal cortex, the anterior cingulate, and the thalamus to `normals`.
- Frontal lobes: Executive functioning problems.
- A connection between the dorsolateral prefrontal cortex and disorganized symptoms?
- The ventrolateral prefrontal cortex is associated with negative symptoms.
- The medial prefrontal activity is associated with positive symptoms (music memory and emotions meet).

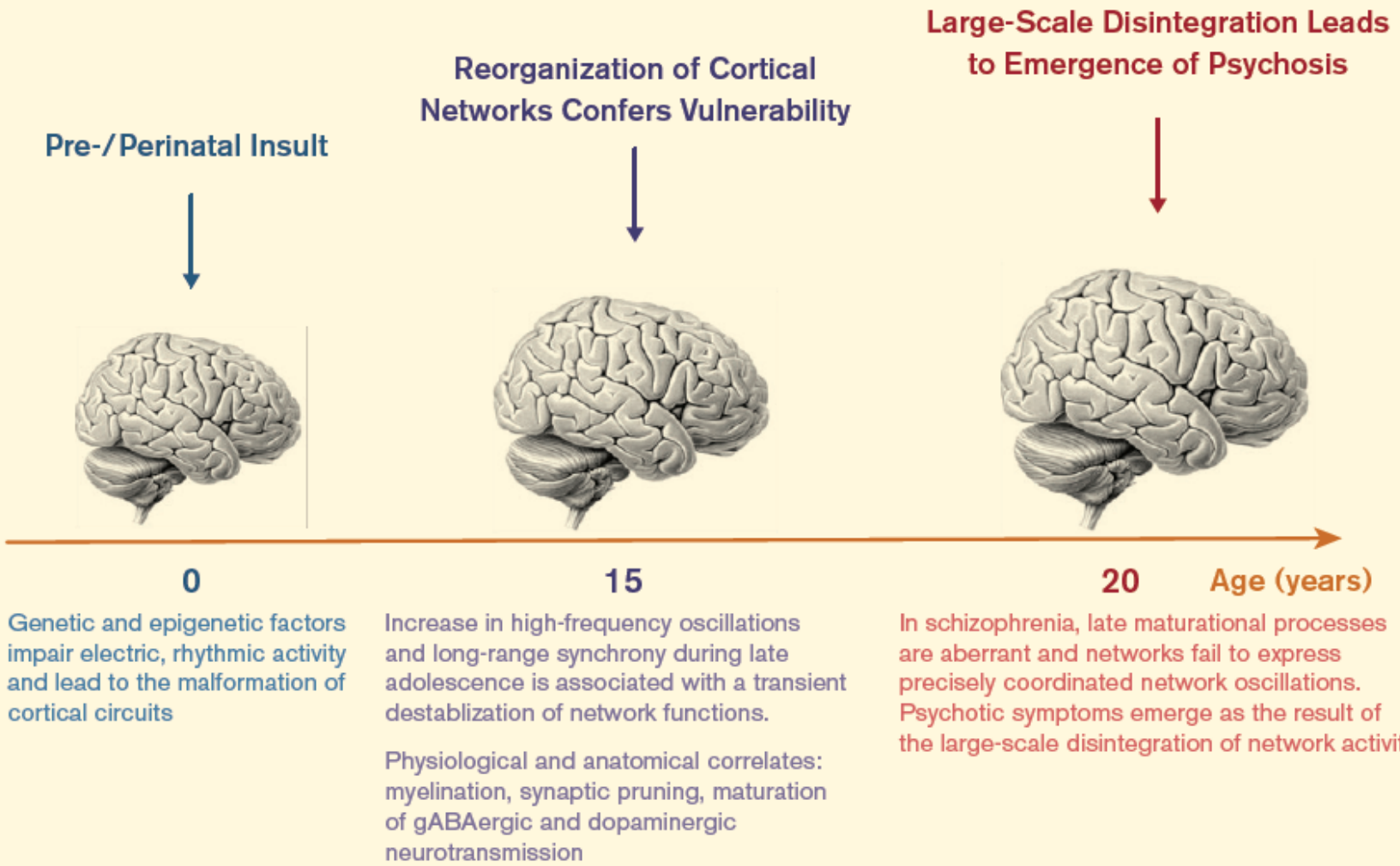
- However, none of these findings are consistent.
- The most common abnormality amongst patients is enlarged ventricles, particularly in the medial temporal lobes of the brain. This is confirmed using MRI scans.
- Harrison (1995) believes that these abnormalities occur before the onset of schizophrenia, implying that they are more likely to be a cause than an outcome of the disorder.
- Since the abnormalities in brain structure do not increase over time, it appears that the problems are due to a failure of the brain to develop normally in the first place.

- One criticism- not one pattern of damage seems to correlate with the disorder. Perhaps, this should not be surprising, given the variety of symptoms associated with schizophrenia.
- But…certain damage is associated with certain symptoms:
  - Damage to the temporal lobe is associated with some of the positive symptoms whereas damage to the frontal lobe is associated more with the negative symptoms.
- Any such differences between the brain of a 'schizophrenic' and 'non-schizophrenic' brain are so small that it is not possible to detect them in the individual. They only become apparent if groups of schizophrenic and non-schizophrenic brains are compared.

Brain changes in schizophrenia

- Cortical networks begin in utero and continue following birth.
- However development is not continuous and a major reorganisation occurs in adolescence (Uhlhaas et al., 2012) and a final reorganisation of EEG activity in specific sites such as the parietal and occipital electrodes.
- Gilmore et al. (2010) performed Ultra Sound and MRI scans before and after birth for a control group and babies of SCHZ mothers.
  - No difference prior to birth, but more gray matter, more CSF and larger ventricles after in males.
  - Suggests that the endophenotype is present early in life.

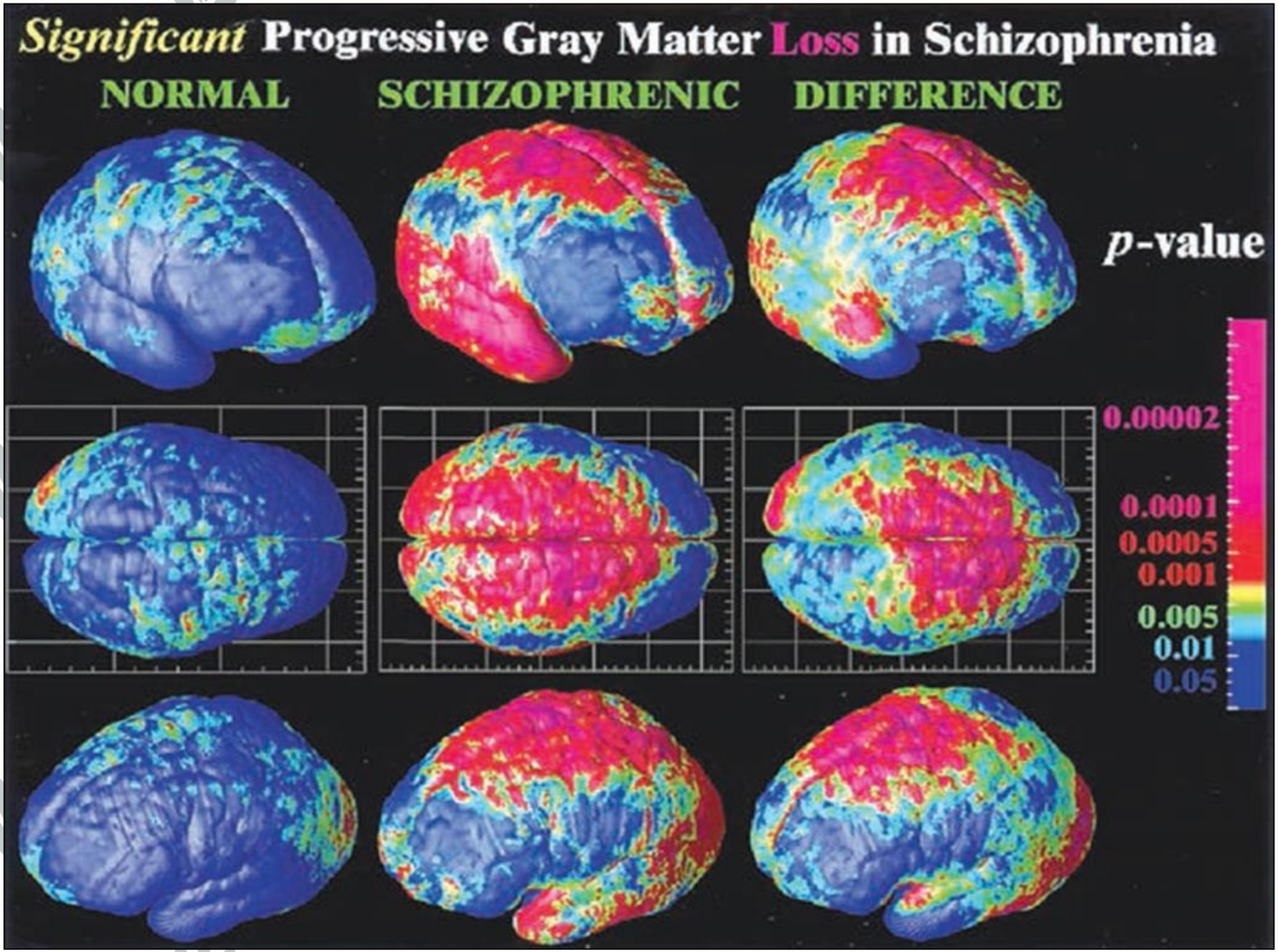
Figure 7-9 Three Critical Periods and Changes in the Physiology and Anatomy of Cortical Processes



SOURCE: From Peter J. Uhlhaas and Wolf Singer. "The Development of Neural Synchrony and Large-Scale Cortical Networks During Adolescence: Relevance for the Pathophysiology of Schizophrenia and Neurodevelopmental Hypothesis." *Schizophrenia Bulletin*, 2011 May; 37(3): 514–523, by permission of Oxford University Press.

MRI and fMRI scans

- **Structural**- reduction in both white and gray matter (Thompson et al., 2001).
- Gray matter reduction- atrophy?
- Possibly not… more of them to begin with and less neuropil between the neurons.
- White matter loss- indication of progression of the disorder.
- **Functional-** when performing a task, our default network is supressed to allow for better performance.
- However, individuals predisposed/sufferers, show inability to show pattern of normal suppression when performing cognitive tasks.
- Also less strong connections between brain areas than `normals` and the strength of the connections is correlated with measures of memory attention etc.


Significant Progressive Gray Matter Loss in Schizophrenia
NORMAL
SCHIZOPHRENIC
DIFFERENCE
p-value
0.00002
0.0001
0.0005
0.001
0.005
0.01
0.05

Viral theory

- More schizophrenics born in late winter or early spring (figures suggest up to 8% more than other times of the year).
- Because various diseases such as colds, influenza, chicken pox etc. also show such a seasonal variation it was suggested that there might be a link.
- Support
- Torrey (1988) viral infection in the mother during the second trimester of pregnancy. Barr et al. (1990) found those in the fifth month of foetal development during the influenza pandemic of 1957 grew up to have a significantly higher risk of developing schizophrenia.
- This has been questioned by others because the effects are not worldwide. This increased risk was only evident in England, Wales and Finland and was not apparent in Scotland or the USA.

Viral theory revisited…

- More recently- Some of our genes developed from viruses and became incorporated into our genetic make up.
- Blomberg estimates 1% of the human genome is made up of these retroviruses. These remain 'dormant' but can be activated by certain other viral infections or by other factors during foetal development or infancy.
- Blood samples were taken from 53,000 pregnant women in the USA during the 1950s and subsequently frozen. Buka (1999) checked the offspring and found 27 schizophrenic sufferers in the Boston area.
- Buka found that their mothers' blood was significantly more likely to contain antibodies (suggesting a viral infection during pregnancy).
- The most common infection found was herpes.

- Some of these quiescent genes are responsible for making proteins which can be detected in the CSF of the brain. Karlsson found genetic material from these viruses in 29% of recently diagnosed schizophrenics. There was no sign in healthy patients.
- The ventricles are hollow chambers filled with CSF. The CSF helps cool the brain, absorbs the waste products and acts as a shock absorber.
- However, it is also clear that the larger the ventricles the less space there is for neurons and brain tissue. Perhaps this is the problem with the brains of some schizophrenics.

Diathesis stress

- Diathesis – a person's genetic predisposition to a particular disorder. Because of their genes, some people are more likely to develop schizophrenia than others.
- However, this alone does not guarantee that they will. (Think of MZ twins, one of whom has the disorder and the other who does not).
- Stress refers to the environmental factors that trigger it, for example high levels of expressed emotion, major life events or a dysfunctional family.
- **Support**
- Tienari (1987) found that in all cases of schizophrenia studied, one or another members of the sufferer's family were disturbed.
- Marcus (1987) Israeli study, all parents of schizophrenics studied had poor parenting skills.

Social and Psychological factors

- Family Models of schizophrenia:
  - Double Bind
  - Expressed Emotion
  - Schizophrenogenic mother

Double bind theory

- Bateson (1956) described the situation were families send out contradictory messages to their children.
- Parents say they care whilst appearing critical or, they express love whilst appearing angry.
- A classic example would be telling the child you'd like a hug and then pulling away when they try!
- Bateson believed that this caused confusion and self-doubt in the child leading to their withdrawal as they lose confidence in their own ability to express themselves.

Schizophrenogenic mother

- **Fromm-Reichman (1948**) a mother likely to produce the disorder in her offspring. Typically cold, domineering conflict inducing, rejecting and very moralistic, particularly about sex.
- Fromm-Reichman believed that such a mother in conjunction with a weak and ineffectual father could 'drive' a child to schizophrenia. Little research evidence has found support for the theory.
- **Although support is limited, it is clear that the families of schizophrenics are often in some way different, showing high levels of conflict and poor communication. However- cause and effect?**
- **To what extent is the schizophrenia a result of these issues and to what extent may it be a cause?**

- **Goldstein & Rodnick (1975)** believed family problems were a cause rather than a consequence. They found that often the family problems pre-dated the onset of schizophrenia.

- **Tienari (1991)** reported that children born to schizophrenic mothers and later adopted were far more likely to develop schizophrenia if adopted into a disturbed family. This provides good evidence for the diathesis-stress model; genetic predisposition followed by an environmental (familial) trigger.

Expressed emotion

- High levels of EE are typified by extremes of emotional content in conversations and daily life
- E.g. high levels of hostility and criticism and over concern with others.
- Important in maintaining schizophrenia more than causing it? (Brown et al 1958).
- Schizophrenics returning to such a family were more likely to relapse than those returning to a family low in EE.
- Relapse was particularly high if returning to a high EE family and no medication.
- **This is now well established as a 'maintenance model' of schizophrenia. Treatment of schizophrenia often involves education and training for other family members in reducing their levels of EE.**
- **But...**
- **Some schizophrenics have little or no contact with their families when released back into the community, but their relapse rate does not appear to be any lower as a result.**

Stress and Schizophrenia

- Another explanation is that schizophrenia is caused by stressful life events.

- **Day et al. (1987)** carried out a study across several countries. Schizophrenic sufferers tended to have experienced a number of stressful life events in the few weeks before the onset of schizophrenia.
- But… are there two possible interpretations of these findings?

- Not all evidence supports the role of life events. **Van Os et al. (1994)** reported no link between life events and the onset of schizophrenia.
- Patients were no more likely to have experienced a major life event or not, in the three months prior to onset of schizophrenia (retrospective study).
- A prospective part of the study demonstrated that patients who had experienced one, went on to have a lower rate of relapse!
- Any evidence that does suggest a link is also correlational.

Social causation hypothesis

- This explanation tries to explain why schizophrenia is more prevalent in the lower social classes.
- It argues that people in the lower social classes tend to experience more stressful lives because of poverty, unemployment, poorer physical health etc.
- Stress is also likely because of social and racial discrimination. The high level of stress makes people more prone to schizophrenia.
- However, **social drift hypothesis** would suggest that People affected by schizophrenia may be less able to hold steady or demanding higher-paying jobs, consigning them to lower incomes thereby increasing stress levels and leaving them susceptible to lapsing into a schizophrenic episode.

Behavioural theories

- Conditioning: Ullman & Krasner (1969): believed that strange behaviour is inadvertently reinforced by others. For example, the staff in psychiatric hospitals paying more attention to those showing the worst symptoms.
- Labelling theory: Scheff (1966). Children who for whatever reason withdraw into an 'inner world' are labelled because of their bizarre behaviour. This leads to attention, such as sympathy, which acts to reinforce the behaviour and causes the person to seek further attention by behaving even more strangely.
- Social learning: Watching others being rewarded for behaving strangely.

- Some of the strange behaviour of schizophrenics can be modified using behaviourist methods such as being reinforced for more appropriate behaviour.
- BUT SLT does not explain how people can develop schizophrenia when there has been no chance to observe schizophrenic behaviour.
- It is possible to see how observable behaviours such as motor disturbances can be acquired in this way.
- However it seems unlikely that hallucinations, delusions and disturbances of thought could be acquired through reinforcement.

Cognitive explanations

Traditional explanations

- Cognitive psychologists believe psychological disorders result from **irrational thinking**, which leads to abnormalities in feelings and behaviour.
- The **delusional beliefs** can be explained as attempts by the patient to make sense of their experiences.
- For example, if a person loses the ability to distinguish between their own inner speech and speech heard from others (as the 'self-monitoring' approaches to schizophrenia suggest) they may experience a voice (actually themselves) giving a running commentary on their behaviour (supported by neuroimaging studies).

Frith`s model

- We are normally able to filter incoming stimuli and process them to extract meaning.
- However for schizophrenia sufferers it is believed that these filtering mechanisms and processing systems are defective.
- Frith distinguishes between conscious and preconscious processing.
- Conscious processing is the highest level of cognitive functioning that we are aware of. It has a limited capacity so we can only carry out one task at a time.
- Preconscious processing, takes place without awareness and is automatic allowing us to carry out many tasks at any one time (default mode).

- Usually only important information arrives into conscious awareness.
- Frith proposes that in sufferers, the attentional filter breaks down, the unimportant information gets in and is perceived as important.
- She believes that this is cause of delusions and auditory hallucinations.
- If the conscious/preconscious filter is defective, it is possible that we misinterpret non-speech sounds as speech and experience them as voices.

But…

- Cognitive models cannot explain why the voices heard are so negative or abusive.
- But, the cognitive approach can explain mainly positive symptoms.
- Cognitive explanations could clarify why delusions are often influenced by cultural factors- i.e. a French schizophrenic might think he is Napoleon whereas a British one might think he is Nelson.
- It has given rise to CBT which seems to improve the outcome for many schizophrenics (see therapy) and has no side-effects.

- In an attempt to reconcile the biological and psychological explanations for schizophrenia, several references have been made to lifestyle factors. For example,
- Being in a minority group is thought to raise the likelihood of an individual developing schizophrenic symptoms.
- As is the idea that people exposed to urbanicity for 15 years or more, are at a higher risk of developing schizophrenia than those who live in rural areas.

- **Fernando (1988)** found that overall, Afro-Caribbean people in the UK are between 2 and 7 times more likely than the general population to develop schizophrenia.
- These populations are at much less of a risk in situations where they become majority populations.

- **Pedersen & Morten (2001)** found that individuals who spent their first 15 years of life in a highly urban area were nearly three times as likely to be diagnosed with schizophrenia, compared with people who grew up in rural areas.

- **Mortensen et al. (1999)** investigated place and season of birth for a Danish cohort of 1.75 million. There was a clear relationship between urbanicity and risk of hospital admission for schizophrenia.
- **Faris and Dunham (1939)** found admission rates for schizophrenia in Chicago were higher in inner city neighbourhoods than towards the periphery of the city.
- **Boydell et al. (2001)** demonstrated that as the proportion of non-white ethnic minorities in a neighbourhood decreases, the rate of incidence of schizophrenia increases (for non-whites).

- **Tienari et al. (1990**) a **prospective study**-
  - 171 mothers had a child adopted before the age of four.
  - The adoptive families were classified as either **healthy**, **mildly disturbed** and **severely disturbed**.
  - Over the course of years, the children were tracked and mental health status assessed.
- None of the adopted children raised in healthy families developed schizophrenia, 9% raised in `mildly disturbed` families did and 11% did in severely `disturbed families`.
  - This suggests that a well adjusted family protects children who may be predisposed, whereas a disturbed environment encourages the predisposition to express itself.
- This provides evidence to support the diathesis stress explanation of schizophrenia.

Where are we now? Tentatively putting it together

- The last decade has seen a re-emergence of the focus of immune responsivity to early environmental stressors through the use of GWAS.
- The belief is that genetic and environmental interactions contribute to cognitive deficits which are the hallmark of schizophrenia.
- Elevated antibodies and proteins are often associated with cognitive impairments, believed to be as a result of genetic abnormalities in immune function markers.

Inflammation and the neural diathesis stress hypothesis of schizophrenia

- So… we are all familiar with diathesis stress.
- Walker & Diforio (1997) identified the HPA axis as the mediator between environmental stressors, vulnerabilities (pre/perinatal) and the manifestation of stress.
- The immune system is implicated because of the glial cells that it contains and in particular the microglia, as they are the primary immune cells of the CNS.
- Microglia are affected by a number of stressors; restraint, social defeat, maternal separation, social isolation.
- The microglial expression of IBA-1 (microglial density) is particularly evident in regions implicated in schizophrenia, the hippocampus, amygdala, nucleus accumbens and PFC.

Glucocorticoids and the glucocorticoid receptor.

- The role of glucocorticoids in the stress response is well know and it affects most immune cells including microglial responses.
- Glucocorticoids can limit the duration and amplitude of the microglial response and as such prenatal infection, neonatal infection and maternal stress can all activate microglial densities in animal models.
- Microglia can be both protective and pathological. i.e. neonatal infection in rats can lead to a blunted response in adulthood.
- Conversely, priming of microglia refers to an exaggerated response from repeated exposure. Although this does normalise later, subsequent exposure to an inflammatory stimulus will again lead to an exaggerated response in adulthood. (Think critical periods).

So…
What can you conclude?

- Your seminar task:
- Plan an essay outline to consider the aetiology and development of schizophrenia, considering the evidence for both environmental and neurological factors.
- Next – Treatments for schizophrenia.

Treatments for Schizophrenia/Psychosis

- A systematic review of remission rates suggests 17-78% remit in first episode and 16-62% remit in second/multiple episodes, with remission highest in those taking second generation (atypical antipsychotic) medication, with early intervention (AlAqeel & Margolese, 2012).
- Other studies show that 81% relapse within 5 years, with 78% of those having a second relapse in that time.
- Around 50% will be hospitalised (Moilanen et al., 2013) and problems with attrition, insight and non-adherence is as high as 49% (Lacro et al., 2002).

Treatments for schizophrenia

- Traditionally custodial care or hospitalisation were the main interventions available until the advent of antipsychotics in the 1950`s and the newer second generation neuroleptics in the 1980`s.
- However, they are not without their drawbacks:
  - Side effects with both
  - Not a cure; suppress not eliminate the symptoms
  - Lifelong use of medication
  - 25% patients develop tardive dyskinesia
  - 50% stop medication within the first year

Treatments for schizophrenia

- A multi-faceted approach of both acute and chronic episodes must be planned for.
- Anti-psychotic drugs are the first port of call, and can be classed as first or second generation.
- Double blind, placebo controlled studies have demonstrated their efficacy (Haddad et al. 2009). 50% of medicated patients see improvement within 4-6 weeks, whereas placebo controls often deteriorate.
- Conley & Kelly (2001) 25% see no improvement, with 30-40% being partial responders.

First and second generation medication

- Work by reducing the severity of psychotic symptoms.
- Individuals are less bothered by troublesome thoughts.
- Motor side effects can occur (EPS) extrapyramidal symptoms and tardive dyskinesia.
- Act by blocking dopamine receptors in cortex and limbic structures (Factor, 2002). Second generation affect serotonin, norepinephrine and acetylcholine receptors too.
- However contradictory research from new drug AMISULPRIDE (Leucht et al., 2009) which does not affect serotonin receptors.

First and second generation medication

- The second generation medications are considered better than the first generation because they selectively target certain D2 receptors and influence the serotonin receptors in ways to make the therapeutic effects more specific (Worrell et al., 2000).
- There is less risk of relapse, fewer side effects, lower levels of motor disturbance and more treatment compliance.
- However, they can affect immune functioning, lead to weight gain, produce extra pyramidal side effects and many RCT`s find no difference in treatment efficacy between the first and second generation drugs.

Some medications and their effects

Drug class	Generic / trade name	Side effect - EPS	Side effect- Weight gain	Receptor D2	Receptor 5HT 2a
First generation	Chlorpromazine haloperidol	** ****	* *	** **	* *
Second generation	Clozapine Risperidone olanzapine	*/- ** *	**** ** ****	** *** ***	**** ***** ****
	Quetiapine Amisulpride	*/- *	** **	** ****	*** -

Psychological therapies

- **Social skills training:**
- Given the behavioural, emotional and cognitive deficits evident in sufferers, social interaction can be problematic; it may be difficult to lead a normal life and leave individuals feeling isolated.
- Social skills training involves the use of modelling, role play and positive reinforcement to equip people with transferrable skills.
- This has the added benefit of maintaining contact with outreach groups or supervisors.
- A specific type of group is IPS: individual placement support, which had led to significantly higher rates of work and wages compared to other programmes (Bond, Drake & Becker, 2012).

CBTp – CBT for Psychosis

- Due to the lack of insight into their illness, CBT was originally believed to be inappropriate. But given the growing body of research indicating that psychological processes are involved in the generation and maintenance of psychosis, (e.g. voices) CBT can be used to target these.
- Morrison (2001) argues that many individuals with schizophrenia have a bias towards interpreting the intrusions as threatening, causing a viscous cycle producing more hallucinations and in turn increasing their negativity.
- One interpreted people engage in safety behaviours which further increase the frequency of the hallucinations.

- CBTp is used in several ways-
- (1) to challenge delusional beliefs
- (2) to develop non-psychotic meanings for symptoms such as the voices
- (3) to reduce the negative symptoms by challenging the low expectations
- (4) by helping the sufferer to adjust to reality in the outside world
- (5) by helping with medication compliance
- (6) it can also be extend to `reattribution therapy`.
- RCT`s show modest effect sizes, but no better than other therapies, but works well when combined with medication.

Other forms of psychosocial treatment

- Family Orientated Aftercare
- From EE, improving coping skills of family members, education and reduce criticism, supported by medication as outpatients
- Cognitive Enhancement Therapy, Cognitive Remediation Training, Personal therapy:
- The practise of cognitive tasks to improve cognitive disability, specifically for cognitive related deficits and to adjust to the outside world.
- Assertive Community Treatment (combination treatments) via multidisciplinary teams.
- Institutional programmes continue to be important.