

HOW DOES SCHIZOPHRENIA OCCUR AND CAN DELUSIONS BE PROTECTIVE TO THE PERSON? A BIRD'S EYE VIEW ATTEMPTING TO INTEGRATE THE NEUROBIOLOGY AND PSYCHOLOGY OF SCHIZOPHRENIA

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SUMMARY

This short paper is an attempt to integrate what we know about the biological development of schizophrenia. It attempts to integrate Neurodevelopmental, Dopamine, Glutamate, Salience and Psychological theories of the development of schizophrenia into a unitary whole, and thus to illustrate how these theories relate together. It is a summary of a much larger work, presently in preparation, done for the purposes of the present conference.

It attempts to describe the biological development of schizophrenia, and thence the delusions and hallucinations which play a part in it symptomatically.

Key words: salience - Dopamine – Glutamate - cognitive biases - schizophrenia

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INTRODUCTION

Schizophrenia is a complex condition with a complex etiology. Here we briefly attempt to integrate Neurodevelopmental, Dopamine, Glutamate, Salience and Psychological theories of the development of schizophrenia into a unitary whole, and thus to illustrate how these theories relate together.

Genetics

From the genetic point of view, it is now generally accepted that schizophrenia occurs because the inheritance of polymorphisms of many genes, each one of which has a small effect (Craddock 2005a, b), although it is also accepted that major mutations may also occur (McClellan 2007). Each of the single nucleotide polymorphisms which are involved will have a specific effect; some, such as COMT or BDNF will have a specific known role as an enzyme involved in neurotransmitter systems, or as a trophic factor in neurogenesis, others, such as Neuregulin or DISC appear to have roles in the development of psychosis (Craddock 2005).

Furthermore, there are epigenetic influences, some of which include infection with viruses in pregnancy, foetal and birth hypoxia, and brain injuries which also play a part in the development of schizophrenia (McCreadie 2000, Perrin 2007).

Given the above, it comes as no surprise, that, given that multiple different abnormal polymorphisms can be present in any one individual, and that each of these can cause abnormalities at different points of the whole sequence of events which constitute normal brain development, there will be multiple abnormalities at mole-

cular and cellular level in each individual, and these will cause the description of several endophenotypes, each somewhat different from each other (Marengo 2000, Rapoport 2005). Indeed, the surprising thing is that groups of individuals can in fact be brought together as having a number of common syndromes, which can be classified into the classes of psychotic illness, such as schizophrenia, schizoaffective disorder, bipolar disorder and the other psychoses (Figure 1).

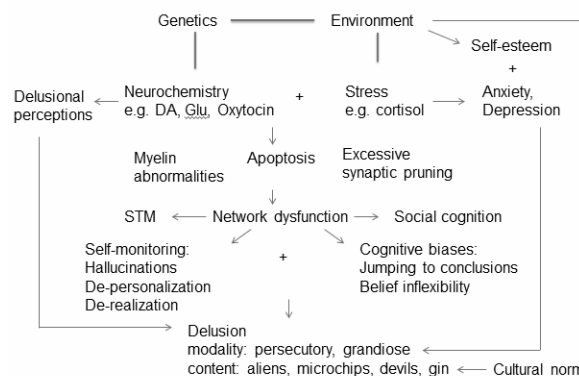


Figure 1. Main system relationships which eventually give rise to positive symptoms of schizophrenia (delusions)

The Neurodevelopmental Theory of Schizophrenia

Furthermore, the many single nucleotide polymorphisms involved will come into play at different times, as they come to affect the development of the adult brain, so that the illness process develops over time, and can be observed, by such methods as MRI (Voxel Based Morphometry) to measure grey matter loss, Tensor

diffusion imaging to measure white matter damage). This allows the progress of the illness to be observed over years, such that some have argued for the possibility of staging the illness, based on Neuroimaging and clinical findings (Agius 2010).

When Weinberger first proposed the Neurodevelopmental Theory of Schizophrenia, it was assumed that the process of abnormal neurodevelopment began at birth – witness the delayed developmental milestones of patients who later developed schizophrenia (Marenco 2000, Rapoport 2005). However later it was realised that a second ‘hit’ occurred during the development of the adult brain in the teenage and early twenties years (Velakoulis 2000, Selemon 2015). This second hit was said to involve several factors, including Synaptic pruning (Keshavan 1994, Hoffman 1989), Apoptosis (Gassó 2014), and abnormal myelination (Catts 2013). All of these processes are amenable to numerous different abnormalities, each of which are related to different single nucleotide polymorphisms as described above.

Again the consequence of this is that there will be numerous potential points at which abnormality, and therefore vulnerability to and consequent illness can occur, and thus there will be a marked heterogeneity in symptoms, and also in the trajectory of the illness, so that some will have a remitting relapsing course- stress being an important factor in causing relapse (the stress vulnerability model of psychosis) - and others having an ongoing course with multiple exacerbations leading to early chronic morbidity and mortality (Zubin 1977). Indeed it is suggested by some that late schizophrenia may represent not simply a neurodevelopmental but also a neurodegenerative illness, and others have suggested that schizophrenia may not only be a disease of the brain, but also in fact a wider condition of the whole body linked with early aging (Papanastasiou 2011).

Abnormal Salience and the Dopamine Hypothesis

All the above does explain the developing anatomical abnormalities which can be observed by MRI and other techniques in patients with psychosis, however it does not explain the development of Hallucinations and Delusions. In order to do this, one must consider the transmission of information in the brain by several neurotransmitter systems.

Several Neurotransmitters can cause hallucinations. The different nature of hallucinations caused by amphetamines (noradrenergic and dopaminergic systems) and LSD (serotonergic system) illustrate that different neurotransmitter systems can be involved in the development of psychotic illness, including schizophrenia.

That dopamine is involved in the development of psychosis has been known since it was found that blocking of the D2 receptor by typical antipsychotics can alleviate hallucinations and delusions.

Kapur has pointed out that in fact, the presence of excessive dopamine can lead to the experience of abnormal salience of different perceptions. In the acute situation, this would lead to specific objects becoming more salient than others, while other objects would, by contrast, become less salient (Howes 2009, Kapur 2005).

Thus, if delusional perception (A front rank symptom of schizophrenia, which involves both perception and belief) were taken as an example of an acute psychotic episode, then the person experiences a general feeling of unreality and blurred perception, while one object stands out before him, hence it acquires a special meaning. It is suggested that the perception is caused by a surge of dopamine, which caused, by the consequent abnormal salience, the abnormal experience- which will feel entirely real to the patient.

In a more chronic situation, it is postulated that the same thing happens, an on going increased supply of dopamine neurotransmitter causes an ongoing over stimulation of the downstream postsynaptic glutamatergic neurons in the frontal cortex maintaining the ongoing hallucinatory and delusional state. The dopaminergic neurons involved in the production of hallucinations and delusions (positive symptoms) are within the mesolimbic system.

Thus, Dopamine does not act alone in causing hallucinations and delusions. The dopamine system modulates Glutamate neurons in the frontal cortex which form a number of functional units or networks. One of these is a salience network, and it is this which is responsible for the perception of salience (Gradin 2013).

A large body of work suggests that disruption of the synchronization of large-scale networks could give rise to specific schizophrenia symptoms. Large-scale networks include the salience network, which is anchored on the anterior insula, and enables the switch between dynamic brain states, such as between the central executive (CE) and the default-mode network (DMN), which are anchored to the DLPFC (Palaniyappan 2012).

Cognitive Defects and The Glutamate Hypothesis

Cognitive defects have always been known to be an important part of the psychopathology of schizophrenia. They have been known to be present even in the prodrome of psychotic illness.

It is postulated that these cognitive defects occur because of the involvement of the glutamatergic neurons in the frontal cortex, so that they are not amenable to treatment with D2 Blockers –that is, antipsychotics. The concept of lack of Dopamine in the mesocortical system in the frontal cortex (hypofrontality) has given way to the more accurate description of Disconnectivity, reflecting the idea that there are a number of functional units in the frontal cortex and there is impaired connectivity between them. All of this has led to the hope that medications which work on the glutamate system may,

catapults the formation of delusions, and the latter influences its modality (emotionally-consistent account).

Cognitive Biases in Schizophrenia

Several cognitive biases have been implicated in schizophrenia, some of which include: jumping to conclusions (JTC), need for closure (NFC), intolerance of ambiguity (IA) and intolerance of uncertainty (IU), feedback sensitivity (FS), bias against disconfirmatory evidence (BADE) and bias against confirmatory evidence (BACE). More research is necessary to define the relationship between these biases. Another important cognitive issue with schizophrenia is belief inflexibility.

It appears that abnormal salience is implicated in the origin of these cognitive biases.

It also appears that Hypersalience and Hypofrontality lead to jumping to conclusions and formation of delusions.

Formation of delusions – a Bayesian approach

A Bayesian approach has been taken to understanding delusion formation. “Although a failure of self-monitoring captures well the features of the passive experiences that characterize many positive symptoms, it does not seem very relevant to delusions; for example, the sudden onset of a belief that my neighbour is trying to poison me does not have an obvious link to abnormal sensation. For these positive symptoms it seems more plausible that the underlying problem lies with the formation of beliefs, rather than with the perceptions from which the beliefs are derived. Although logical reasoning does not seem to be markedly impaired in patients with schizophrenia, there is evidence of problems with probabilistic reasoning. Probabilistic reasoning is associated with a Bayesian approach to the study of belief formation (Feinberg 2006). Within this framework, a belief is the subjective probability that some proposition about the world is true. This probability is continually updated by new evidence. Abnormal belief formation occurs when beliefs are not updated appropriately on the basis of new evidence (Hemsley 1986, Fletcher 2009) (Figure 5).

Emotions and self-esteem

The way in which people with schizophrenia make sense of their chaotic environment, we argue is fraught by cognitive biases, but is ultimately reliant on their emotions, and self-esteem (Freeman 2013), and also their cultural background and previous real experiences, which can be transformed by metaphorical meanings and reflect the content of delusions (Rhodes 2004).

The relationship between emotions, self-esteem and delusions has been extensively researched, and no consensus has yet been reached.

The proponents of the emotion-consistent accounts argue for a direct role of emotion in the development of

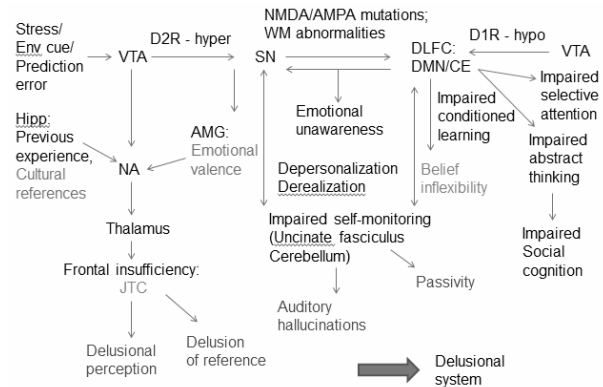


Figure 5. A schema of how aberrant salience and network dysfunction lead to the formation of positive and negative symptoms, cognitive biases and ultimately a delusional system

delusional beliefs. For example, Freeman et al. (2001) argue that persecutory delusions reflect the true emotional state of an individual, such as feelings of anxiety, depression, vulnerability, and low self-esteem. Similarly, Freeman (2003) alongside Smith (2005) suggest that Grandiose Delusions may relate to current positive emotion and preserved areas of self-esteem. Feelings of elation and mood-congruent positive beliefs are proposed to further reinforce positive self-concept and subsequently lead to development of Grandiose Delusions (Smith 2005).

Defence theories on the other hand suggest that delusions serve a defensive function, protecting an individual from distressing emotions and low self-esteem. Defence theories of persecutory delusions originate from Freud's psychoanalytic formulations of paranoia, which propose that ideas incompatible with the ego are projected into the external world (McKay 2007). Contemporary defence theories postulate that individuals with persecutory delusions develop delusions as a consequence of attributing negative events to the actions of other people, a strategy employed to protect them from low self-esteem entering their consciousness (Bentall 1994, Bentall 2001).

According to Neale, mania and Grandiose Delusions are possible strategies for reducing the discrepancy between these two self-representations, and for avoiding distressing cognitions and low self-esteem" (Grbic 2013).

Mountoussis (2007) suggests that the reason why patients with paranoid delusions explain their negative life events in a persecutory way is to protect their self-esteem.

He also shows that patients with paranoid delusions sustain their delusions by acting under the influence of the Conditioned Avoidance Response. Thus patients endorse safety (avoidance) behaviours, which help perpetuate and fix persecutory ideas by preventing their disconfirmation. This defensive function predominates only in the overtly psychotic patients.

The value of delusions

Rokeach illustrated the value of grandiose delusions by his experiments. It appears that as humans, they too have a very potent survival instinct, which however hinges on a constructed concept of self. Thus, like any human that must protect its identity, they too would go to any extreme to vouchsafe it.

The patient himself knows that his personality is gradually disintegrating and that he lives in chaos and does not cope and yet he has the specific status that something is special about him. His idea, perhaps started by a delusional perception, supports his self-esteem. His delusions of grandeur are a defence mechanism again having to suffer poor self-esteem in a chaotic world. His delusion may be the last prop to sustain his self-esteem in a chaotic world even though in order to maintain that prop he may appear out of touch with what we would call reality. Hence, if we should take that prop away, this may leave him with no defence mechanisms left available. One needs therefore to be very judicious about challenging a patient's grandiose delusions because if we expose the misery of his situation it may lead to the patient rediscovering a sense of worthlessness, losing all hope and even considering suicide.

Thus the way to help people with delusions is not to challenge them, but to focus on increasing self-esteem and fostering a positive view of self. This should include managing self-esteem fluctuations and developing a more stable self-concept, whilst pursuing opportunities for self-growth. It may be helpful to explore alternative ways of gaining an expanding sense of self such as through developing better relationships, using positive coping strategies and managing overwhelming emotions. "Based on the understanding of the importance of relationships and their emotional impact on the onset of GDs, Cognitive Analytic Therapy (CAT) may be a helpful therapy. This therapy could assist clients' understanding of unhelpful relationship patterns, such as high expressed emotions, and the impact of emotional context of relationships on their self-concept and self-esteem, whilst providing them with strategies to break these patterns and manage the overwhelming emotions" (Grbic 2013).

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