

The Pathogenesis of Schizophrenia and Outlines for its Suggested Treatment Accordingly

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Introduction

The genesis of schizophrenia has been studied for a very long time. The role of dopamine in “the biochemical contribution to the aetiology of schizophrenia” as “the dopaminergic systems hypothesis” [1] was an early step forward in uncovering the mechanism of the illness. This paper sets the dopaminergic systems hypothesis and the perinatal hypoxia hypothesis into place, and assigns roles for the A10 nucleus and the re-defined nucleus accumbens, which arguably does not require rewards to fulfil its role of registering wellbeing. The great unhappiness of schizophrenic patients is found to be one of the causes of the illness rather than solely its effect, although the distorted psychotic output of the prefrontal cortex is of course also very distressing for the patient. However, means are now available through intensive, supervised care, to treat the patient with individual psychoanalytic psychotherapy and psychodynamic family therapy and medication. The greatest attention needs to be paid to patient safety throughout the treatment.

Fresh Understanding of the Mechanism of Schizophrenia A Proposal for the Pathological Process of Schizophrenia

The A10 nucleus is situated within the brainstem surrounded by nuclei governing the individual’s physiological homeostasis; blood pressure, pulse rate, temperature, oxygen saturation levels of the blood, and respiratory rate are regulated here. The A10 nucleus, too, is arguably a homeostatic nucleus, maintaining the individual’s sense of wellbeing by trying to avoid dysphoria and promoting a sense of positive experience. It promotes dopamine production in the nucleus accumbens via the mesolimbic pathway as a mechanism of promoting euphoria, an effect brought about by drugs of addiction such as amphetamines. The A10 nucleus

innervates several areas via its mesolimbic tract; it innervates the prefrontal cortex to produce dopamine as well as the nucleus accumbens in the limbic lobe. The nucleus accumbens is known as the brain’s reward centre because of its response to drugs of addiction, the appreciation of good experiences and rewards.

Schizophrenic patients have been found [2,3] to experience life in a deeply painful way. Commonly they have lived through objectively terrible experiences that might be upsetting for anyone, but as Sir Aubrey Lewis demonstrated, are also recorded as admitting to horrendous experience beyond anything a healthy person might encounter [4]. Perhaps endogenous and negative symptoms are the most dreadful of all, but Dr Michael Robbins’ treatable paranoid schizophrenic patients also lived through terrible early times [5]. Their thinking was of miserable thoughts, and their feelings were deeply unpleasant and painful. No-one yet knows why their experience is so very, very unpleasant.

The A10 nucleus directs, via the mesolimbic pathway, increasing amounts of dopamine to be secreted, particularly by the nucleus accumbens, in its attempt to promote wellbeing in the suffering individual. Dopamine at the nucleus accumbens is known to increase the sense of wellbeing, from studies of addiction to amphetamines and other substances, causing it to be known as the reward centre of the brain. However, the patient in her environment which is, perhaps, and may be experienced by her as, hostile in some way to her, becomes increasingly and seriously miserable, in the prodromal phase of her illness. She may become introverted, preoccupied and isolated. The nucleus accumbens detects this unpleasant dysphoria as an early stage in its role of establishing appetitive behaviour; in schizophrenic patients, the dysphoria is so intense that it dominates the nucleus accumbens’ responsive glutamatergic connection to the A10 nucleus.

Perinatal hypoxia and prenatal stress lead to increased vulnerability to the development of sensitization to dopamine during adulthood [6,7]. Repeated exposure to dopamine in schizophrenic adults may lead to materialization of this sensitization [8]; they manifest increased cortical temporolimbic activity, with more thoughts flowing and more labile emotions. Hypoxia also interferes with NMDA (N-methyl-D-aspartate) receptors that implement glutamatergic neurotransmission.

The prefrontal lobe of the cortex is situated near the nucleus accumbens in the brain, further along the mesolimbic tract from this nucleus, and when the nucleus accumbens' dopamine output is increased by the A10 nucleus, so, arguably, is that of the prefrontal cortex. Sensitized to the effects of the nearby excess dopamine, and with its own innervation by the A10 nucleus, the prefrontal cortex malfunctions. Instead of its normal functioning in health of formulating, monitoring and modifying the patient's action plans, in schizophrenia it manifests reduced activity, dysregulation and decreased efficiency, especially in response to exogenous or endogenous stress [9].

When mental breakdown occurs, often in response to stress, the compromised prefrontal cortex can no longer process the patient's increasingly intense and miserable thoughts normally. The patient's profoundly miserable thoughts prevail, but the prefrontal cortex in its parlous state can now only process them unrealistically, through make-shift 'defence' mechanisms, as psychotic thoughts. These psychotic thoughts do not contain their original pain and in this may be thought of as a kind of defence for the patient, and are usually illogical and unrealistic approximations of what the patient is trying to say. Their distortions are studied through the technique of Psychodynamics [10] as a route via the patient's unconscious (at the level of physiological processes in the prefrontal cortex) into the patient's conscious mind (at the level of the main cortical lobes). This eventually may lead to uncovering, by interpreting the patient's spoken thoughts, the causes of the patient's long term experienced acute distress and pain which have remained in their unconscious mind as painful memories, in addition to their current distress. Therapeutically, when this is understood the patient may be helped to resolve her problems.

The neurophysiology of the pathogenesis of schizophrenia may involve glutamatergic neurotransmission, which occurs via NMDA receptors and is vulnerable to hypoxia [8]; it is widely held that NMDA neurotransmission may be deficient in some way in schizophrenia [8]. Dopaminergic neurotransmission from the ventral tegmental area (A10 nucleus) to the nucleus accumbens is regulated by the prefrontal cortex [11] and the neurotransmitter serotonin [8,12,13]. The glutamatergic connections between the prefrontal cortex and the nucleus accumbens and between the prefrontal cortex and the A10 nucleus may be negative feedback mechanisms, which are interfered with by hypoxia, including at birth, and by NMDA blockers. This interference may prevent control by the prefrontal cortex of dopamine production at the nucleus accumbens, and of stimulation of dopamine production by the A10 nucleus, where at both sites the prefrontal cortex would

normally act by feedback inhibition from its own mesolimbic dopaminergic innervation. The nucleus accumbens' own glutamatergic connection with the A10 nucleus, indicating to this nucleus the patient's dysphoria, would normally initiate dopamine production; but NMDA blockers and hypoxia, that interfere with this specific connection and would inhibit the nucleus accumbens' dopamine production, have a more powerful effect than this through their inhibition of the prefrontal cortex's negative feedback pathways, and lead instead to excess dopamine being produced by the nucleus accumbens. NMDA blockers lead to excess dopamine production and the appearance of schizophrenic symptoms. It would also seem, accordingly, that in many cases of schizophrenia itself where the prefrontal cortex has been damaged by dopamine sensitization, this would interfere with both of the prefrontal cortex's feedback mechanisms, an effect which may override inhibition of the nucleus accumbens' own link to the A10 nucleus, and so result in excess dopamine production and schizophrenia.

A further influence on dopamine production may be serotonin, which modulates dopamine neurotransmission at the prefrontal cortex, the nucleus accumbens and the A10 nucleus [8]. Lowered serotonin levels accompanying dysphoria may reinforce the nucleus accumbens' message to the A10 nucleus. In addition, small Gamma-amino-butyric-acid-ergic (GABA-ergic) interneurons are found to be deficient in the prefrontal and cingulate cortices of schizophrenic patients [14], another probable source of malfunctioning in the prefrontal cortex of the schizophrenic brain. Further influence on the mechanisms of schizophrenia is from the amygdala, which is known to regulate dopamine release in the nucleus accumbens [15], and may provide input regarding the patient's fear and anger at their experience of their representational world.

Neuroimaging shows that in schizophrenia cerebral perfusion of the prefrontal cortex and the anterior cingulate cortex both correlate with psychomotor poverty symptoms [16]; it shows also decreased connectivity between the anterior cingulate cortex, which is involved in negative symptoms, and the left dorsolateral prefrontal cortex in schizophrenia. Connectivity is also shown on neuroimaging to be decreased between the prefrontal cortex and the temporal lobe and between the prefrontal lobe and the thalamus and cerebellum [17]. These deficits of the prefrontal cortex may be visualised in context by neuroimaging, and seem to confirm the malfunctioning of the prefrontal cortex in schizophrenia which leads to the confused spoken language of the schizophrenic patient.

Summary

Two environmental elements can eventually precipitate schizophrenia, especially when they coincide in an individual: 1) enduring, very miserable, or intolerable experience of an environment that creates semi-permanent intense dysphoria in the patient, and 2) sensitization to dopamine and subsequent malfunctioning of the prefrontal cortex through environmental factors such as perinatal hypoxia or prenatal stress.

The two main neurophysiological components of schizophrenia are: 1) the very miserable neocortical and limbic lobe thoughts

and feelings which, registering severe dysphoria in the brain's wellbeing centre, the nucleus accumbens, causes it to indicate this through its glutamatergic connection to the homeostatic A10 nucleus in the brainstem and consequently receive via the mesolimbic tract its instructions from the A10 nucleus to greatly and persistently produce dopamine, to try to improve the patient's experience of wellbeing; and 2) the prefrontal cortex which, being sensitized to dopamine, is exposed to large amounts of dopamine from the nearby nucleus accumbens and its own innervation by the A10 nucleus, and consequently malfunctions, only being able to produce illogical and unrealistic, psychotic language as the patient's action plan. This is the psychotic output of the dopamine-sensitized and -exposed prefrontal cortex resulting from distressed inputs from the neocortex and the limbic lobe caused by the patient's very miserable experience of her lifelong representational world, and it forms the basis of the diagnosis of schizophrenia, together with other symptomatic factors.

New Evidence for the Proposed Healing Process

Evidence that psychoanalytic psychotherapy can structure the mind of a schizoaffective patient from her previous psychotic disorder is found, together with its illustration, as a case study of a 28 year old female patient [18]. This structure, derived from the data derived from this case study through conceptual psychoanalytic research [19], was the structure of her representational world [20]. The representational world is the representation within their preconscious mind of what is known to a child, or an adult, about the world around them as they gradually develop among different environments. The representational world of this 28 year old patient was painful and frightened and frightening. Subsequent research showed [3] that the representational worlds of two further, paranoid schizophrenic patients [2,3] demonstrated pain, fear, violence, manipulation and distress.

Evidence that psychoanalytic psychotherapy can resolve schizophrenia and schizoaffective disorder is found in the case report of the successful treatment of the 28 year old female patient with schizoaffective disorder mentioned above [18] and in the reports of two paranoid schizophrenic patients [2,5]. Attention to patients' representational worlds, as below, helps understanding of schizophrenic illness when this is reactive to environmental circumstances, including trauma, rather than endogenous illness that is constitutional in nature [21]. Other unresolved questions, among many, about schizophrenic illness relate to the unknown origins of positive and negative symptoms, explanations for the symptom clusters of the psychomotor poverty syndrome, the reality distortion syndrome and the disorganization syndrome [22], and understanding of the different ages of onset of the illness, between childhood and up to the seventh decade.

Medications may be used during the psychoanalytic psychotherapy of schizophrenic patients as an adjunct rather than its mainstay [2]. This psychoanalytic psychotherapy through interpretations accesses the patient's unconscious mind; but if this is disrupted by medication affecting her brain too much, through sedation or other side effects, then the patient cannot think clearly. The excess

dopamine and malfunctioning prefrontal cortex interfere with thinking in schizophrenia; but, equally much, the patient cannot reveal what is in her unconscious mind to her psychoanalyst if the 'edge of her perception' from which she speaks (where her conscious mind is contiguous with her unconscious mind) via the prefrontal cortex and Broca's and Wernicke's areas of the cortex, has been numbed by the medication.

Evidence in practice for the overall treatment of schizophrenic patients involves a hierarchy of four systems, Dr Michael Robbins' Hierarchy of Systems [2], which he bases on John Gedo's work as a psychoanalyst and author, revealing the potential of hierarchical systems concepts to assist in an expansion of psychoanalytic theory [2,23-26]. The four Systems of this Hierarchy comprise organic (neurophysiological-pharmacological); psychological (psychoanalytic psychotherapy); familial (family therapy); and social (community relationships). These four Systems are the levels of care required to permit the healing of schizophrenic patients as far as they can succeed with their treatment [2].

The four Systems in the Hierarchy of care required can be explained by evidence for the proposed pathological process of schizophrenia:

(i) Neurophysiological-pharmacological:

Excess dopamine is produced in the nucleus accumbens, stimulated by the homeostatic A10 nucleus, and impinges on the prefrontal cortex;

The prefrontal cortex, sensitized to the excess dopamine, malfunctions;

Increased activity of the cortex and limbic system-based emotion due to very unpleasant experience and influenced by excess dopamine distracts and disturbs the patient. Medications suppress excess dopamine.

(ii) Psychological:

Under stress, the overactive cortex, heavily burdened by the patient's miserable thoughts and dopaminergic connections with the A10 nucleus, as well as her painful emotion, cannot produce or externalise normal thinking or activity because the prefrontal cortex is malfunctioning.

The patient's original troubling, unwanted, painful thoughts are externalized by the prefrontal cortex in a distorted, unrealistic form because it is manifesting reduced activity, dysregulation and decreased efficiency: they are psychotic spoken thoughts. Psychoanalytic psychotherapy may resolve her very troubled mental states through regular psychoanalytic sessions with her Psychoanalyst.

(iii) Familial:

Psychodynamic interventions have to enable the family members to "catch up" with the progress their ill member has made, to allow her to speak for herself, and to treat her with kindness and respect.

They eventually learn to relate kindly towards her as she now is, integrated and independent, and accommodate her back into their

midst. She may decide to leave their environment, but on as good terms as possible.

(iv) Social:

When the patient has recovered from feeling so very unwell from her schizophrenia she may be restored into seeing realistically herself and the world and her relationship to it. She may still feel, once her therapy has concluded, remnants of distress such as anxiety, impatience or sadness; but, with renewed effort at living as an independent person, these remaining “corners” of her personality may be “rubbed off” into more comfortable sociability. She becomes able to live more smoothly, fully adjusted to the people around her, and recovered from her schizophrenia.

The prefrontal lobe’s verbal output in schizophrenia is known as ‘psychotic defence mechanisms’. These are distorted thinking that is as near to the meaning of what the prefrontal lobe tries to produce physiologically as it can, but not quite accurately because in schizophrenia the prefrontal lobe’s functioning is compromised. The psychotic language may minimize the intensity of the original thoughts’ pain, but represents in practical terms the best output possible of the prefrontal lobe in the circumstances.

The nucleus accumbens is known as the ‘reward centre’ of the brain; prior to its recognition of rewards, it could also be known as the ‘wellbeing centre’ of the brain, detecting the individual’s state of wellbeing, before any drugs of addiction have been presented to it.

Treatment is indicated at each of the 4 Levels of Dr Robbins’ Hierarchy of Systems:

Neurophysiological-Pharmacological

Quelling the excessive dopamine production instigated by the A10 nucleus in the nucleus accumbens, and also as its own innervation, may enable the sensitized and malfunctioning prefrontal cortex to function more effectively, and so allow the patient to express themselves more accurately. Phenothiazines such as chlorpromazine and trifluoperazine are established agents that achieve this in patients, but some of the more recently developed antipsychotics such as clozapine, risperidone, olanzapine, or aripiprazole are able to bring this about with fewer side effects. The role of medication in the treatment of schizophrenia is to prescribe a sufficient dose to quell psychotic language and behaviour but not so much as to prevent access by the patient to their true, unconsciously held thoughts, or produce side effects.

Individual Psychoanalytic Psychotherapy

Individual psychoanalytic psychotherapy [2] for up to 10-11 years, but usually less, conducted by a psychiatrically trained Psychoanalyst, is the form of psychological treatment that most effectively resolves schizophrenia. This form of therapy gains access to the patient’s unconscious thoughts, even deeper than the patient’s conscious thoughts. The patient’s overactive cortex, burdened by unpleasant thoughts, has not been able to gain normal expression: distorted, psychotic thoughts are being uttered instead, via the inefficient prefrontal cortex, which functions at a level

below the conscious. Psychoanalytic psychotherapy can produce improved functioning here, especially when the dopaminergic excess has been subdued by medication; gradually, with improved functioning, the medication may be reduced.

Interpretations by the Psychoanalyst, directed towards what he knows of the schizoaffective patient’s representational world [18], lead to calming of her psychotic tendencies when carefully made [2,18]. Through this technique he is able to modify or correct the patient’s unrealistic Observations [18], Determine the Orientation of her psychosis, whether of manic Fantasies or grim depressive Facts, or schizophrenic Concrete thinking [18], give her feedback on her Dreams and confirm with her how she might Represent people or other aspects of the world peopling her representational world in a happier light [18], and share her Experiences [18] empathetically as she describes these to him. These elements of the Psychoanalyst’s practice are predicted by the PPCC Theory [18], a conceptual psychoanalytic theory which holds that the stages of the psychoanalytic resolution of schizophrenia may be helpfully illustrated visually. This psychoanalytic theory, as declared by the Shorter Oxford Textbook of Psychiatry [27] as required for a psychoanalytic theory, “is derived from data obtained in the course of psychoanalytic treatment; these data relate to the patient’s thoughts, fantasies and dreams, together with their memories of childhood experiences”.

The patient will be on sufficient medication to prevent excess dopamine from interfering with her production of thought and language via her inefficient prefrontal cortex: but not so much that what she really thinks due to her cortical activity cannot gain access to her prefrontal cortex at all, inefficient though it is. Perhaps it would not be a giant leap for some Psychiatrists to train in Psychoanalysis, as a number do now, with others training as they do currently in Medical Psychotherapy and some in Adult and Community Psychiatry. Schizophrenic patients need all kinds of Psychiatrists at different stages in their treatment, but cannot experience the benefits of psychotherapy as patients with other diagnoses can. All branches of Psychiatric understanding and learning already are doing wonderful work: the psychoanalysis of schizophrenia is a young subject and as Professor Peter Tyrer explains, progress is made in “little shuffles”.

Alternative Forms of Psychological Therapy

Not every patient is suited to the rigours of psychoanalytic psychotherapy. Cognitive behavioural therapy [28] may be effective when delivered with a symptomatic approach within psychosis. A psychodynamic approach has been developed and adopted in Turku, Finland, in therapeutic communities and with selected patients for individual therapy; this treatment is endorsed by both the patients and their families as widely helping patients regarding self-expression and individuation [29]. Motivational interviewing can stimulate schizophrenic patients towards more effort to help themselves. Supportive psychotherapy, social skills development, and work skills development in sheltered employment schemes can all help schizophrenic patients find satisfaction in life at their own best level of enterprise.

Psychodynamic Family Therapy

A schizophrenic patient does well if she makes progress in her psychoanalytic psychotherapy sessions. Through her transference relationship with her Psychoanalyst she begins to see and think more as he does, ie. realistically. Her sense of herself changes as she individuates as a person and differentiates from him, as an integrated person, the person she is.

However, her family still perceives her as she was before her therapy, while very ill; through their own eyes as a small group, they see life through the same or a similar lens as each other, and have become used to seeing life that way. They need help to change their thinking in a similar way to the changes the patient has made in herself in order to become well. She has been thoroughly miserable among them, so they all need help to think differently and accommodate the new health the patient has availed herself of; and this is open to them if only they will accept this idea.

Tact is needed at all times to take care of the individual family members' feelings. Some strange ideas may surface, with collusion, very strong defences and often-aggressive feelings. As maintained particularly by Professor Julian Leff, it is widely considered never correct to blame parents for their childrens' illnesses. Psychodynamic understanding is very helpful in recognizing all these aspects; it is also helpful if two or more experienced staff work together, including the Psychoanalyst, to support each other during the family therapy work while they support all the members of the family. Human nature has to be accommodated, and some pathology may be uncovered. This, within the family, may have been having a serious effect on the other family members. Much discretion and professional skill is required to contain this effect, with a decision whether to inform the family of it or not. Sometimes it may be better not to try to change the family's functioning, with the diagnosis within it, except to help them into better ways of relating to the ill member who is recovering, and to show them quietly but clearly how what is said can over time provoke illness: or, on the other hand, promote family harmony. The patient may choose to leave the family, on the best terms possible.

Social Care in the Community

The schizophrenic patient, once they have become able to function independently as the self they truly are, which is great progress for them in their life, is likely to want to move into a community where they can implement their rediscovered zest for living. A measure of social support should be given to them as they find their way in the community, to help them overcome difficulties as these arise from time to time. Increasingly they become quite able to guide their own life after their successful psychoanalytic psychotherapy and family therapy, and may be able to relinquish medication. Some patients are able to achieve a university degree, get married, or adopt children and bring them up safely and happily. The investment in their lengthy psychological therapy can then be seen to have been successful, as well as entirely beneficial on a humanitarian basis.

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