
TREATMENT OF PSYCHOSIS AND SCHIZOPHRENIA

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Psychosis, and particularly in the form of schizophrenia, is often seen as a serious life altering condition. However, in clinical practice many patients can attain remission or at least substantial remission, which enables them to lead the personal and professional lives they want. While medication plays a significant role, particularly in the acute stages and their aftermath, psychotherapy and social support gain additional prominence in relapse prevention over the long-term. They are also indicated in patients who may not have had a full psychotic episode yet but are at greater risk for one. Work on internal and external communication patterns has shown in individual cases to be very helpful as a psychotherapeutic approach to support the patient in fulfilling own needs and aspirations, while increasing treatment compliance and the overall quality of life. Communication-Focused Therapy®, as developed by the author, offers a theoretical framework and an extensive toolset for this approach to treatment.

Keywords: panic attack, anxiety, psychotherapy, Communication-Focused Therapy®, CFT®, medication, psychiatry

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Introduction

Psychosis is an abnormal condition of the mind that results in difficulties determining what is real and what is not. Symptoms may include false beliefs (delusions) and seeing or hearing things that others do not see or hear (hallucinations). Other symptoms may include incoherent speech and behavior that is inappropriate for the situation. There may also be sleep problems, social withdrawal, lack of motivation, and difficulties carrying out daily activities. In the United States about 3% of people develop psychosis at some point in their lives. Symptoms resembling those of schizophrenia have been described in the Ebers papyrus, an Egyptian medical papyrus of herbal knowledge dating to circa 1550 BC.

The core problem in psychosis that the source of communicated information can no longer be identified correctly. For example, one hears a thought in the outside world or feels that outside events begin to influence the thoughts in one's mind. This leads to situations where the imaginary and the real become confused, and the separation between the outside and the inside world become less clear.

Psychosis

From a diagnostic standpoint, organic disorders were believed to be caused by physical illness affecting the brain (that is, psychiatric disorders secondary to other conditions) while functional disorders were considered disorders of the functioning of the mind in the absence of physical disorders (that is, primary psychological or psychiatric disorders). Subtle physical abnormalities have been found in illnesses traditionally considered functional, such as schizophrenia. The DSM-IV-TR avoids the functional/organic distinction, and instead lists traditional psychotic illnesses, psychosis due to general medical conditions, and substance-induced psychosis.

Primary psychiatric causes of psychosis include the following:

- schizophrenia and schizophreniform disorder
- affective (mood) disorders, including major depression, and severe depression or mania in bipolar disorder (manic depression). People experiencing a psychotic episode in the context of depression may experience persecutory or self-blaming delusions or hallucinations, while people experiencing a psychotic episode in the context of mania may form grandiose delusions.

- schizoaffective disorder, involving symptoms of both schizophrenia and mood disorders
- brief psychotic disorder, or acute/transient psychotic disorder
- delusional disorder (persistent delusional disorder)
- chronic hallucinatory psychosis

Psychotic symptoms may also be seen in:

- schizotypal personality disorder
- certain personality disorders at times of stress (including paranoid personality disorder, schizoid personality disorder, and borderline personality disorder)
- major depressive disorder in its severe form, although it is possible and more likely to have severe depression without psychosis
- bipolar disorder in the manic and mixed episodes of bipolar I disorder and depressive episodes of both bipolar I and bipolar II; however, it is possible to experience such states without psychotic symptoms.
- post-traumatic stress disorder
- induced delusional disorder
- Sometimes in obsessive–compulsive disorder

Dissociative disorders, due to many overlapping symptoms, careful differential diagnosis includes especially dissociative identity disorder.

Stress is known to contribute to and trigger psychotic states. A history of psychologically traumatic events, and the recent experience of a stressful event, can both contribute to the development of psychosis. Short-lived psychosis triggered by stress is known as brief reactive psychosis, and patients may spontaneously recover normal functioning within two weeks. In some rare cases, individuals may remain in a state of full-blown psychosis for many years, or perhaps have attenuated psychotic symptoms (such as low intensity hallucinations) present at most times.

Schizophrenia

The symptoms of schizophrenia usually begin in early adulthood and come on gradually. People with schizophrenia may experience hallucinations (most reported are hearing voices), delusions (often bizarre or persecutory in nature), and disorganized thinking and speech. The last may range from loss of train of thought, to sentences only loosely connected in meaning, to speech that is not understandable known as word salad. Social withdrawal, sloppiness of dress and hygiene, and loss of motivation and judgment are all common in schizophrenia. Distortions of self-experience such as feeling as if one's thoughts or feelings are not really one's own to believing thoughts are being inserted into one's mind, sometimes termed passivity phenomena, are also common. There is often an observable pattern of emotional difficulty, for example lack of responsiveness. Impairment in social cognition is associated with schizophrenia, as are symptoms of paranoia. Social isolation commonly occurs. Difficulties in working and long-term memory, attention, executive functioning, and speed of processing

also commonly occur. John Nash, an American mathematician and joint recipient of the 1994 Nobel Prize for Economics, who had schizophrenia. His life was the subject of the 2001 Academy Award-winning film *A Beautiful Mind*.

Schizophrenia affects around 0.3–0.7% of people at some point in their life, or 24 million people worldwide as of 2011. It occurs 1.4 times more frequently in males than females and typically appears earlier in men—the peak ages of onset are 25 years for males and 27 years for females. Onset in childhood is much rarer, as is onset in middle or old age. This is also diagnostically important because an onset of psychotic symptoms later in life is even more likely to be caused by non-psychiatric medical conditions.

Diagnosis

Schizophrenia is diagnosed based on criteria in either the American Psychiatric Association's (APA) fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM 5)*, or the World Health Organization's *International Statistical Classification of Diseases and Related Health Problems (ICD-10)*. These criteria use the experiences reported by the patient and the observations of behavior and communication made by family, friends and the therapist.

Criteria

The ICD-10 criteria put more emphasis on Schneiderian first-rank symptoms¹ than the DSM-5. The current proposal for the ICD-11 criteria for schizophrenia recommends adding self-disorder as a symptom. Symptoms associated with schizophrenia occur along a continuum in the population and must reach a certain severity and level of impairment, before a diagnosis is made.

The ICD-10 lists the following subgroups of schizophrenia:

- F20.0 Paranoid schizophrenia
- F20.1 Disorganized schizophrenia
- F20.2 Catatonic schizophrenia
- F20.3 Undifferentiated schizophrenia
- F20.5 Residual schizophrenia
- F20.8 Other schizophrenia

¹ In the early 20th century, the psychiatrist Kurt Schneider listed the forms of psychotic symptoms that he thought distinguished schizophrenia from other psychotic disorders. These are called first-rank symptoms or Schneider's first-rank symptoms. They include delusions of being controlled by an external force, the belief that thoughts are being inserted into or withdrawn from one's conscious mind, the belief that one's thoughts are being broadcast to other people and hearing hallucinatory voices that comment on one's thoughts or actions or that have a conversation with other hallucinated voices.

- F20.9 Schizophrenia, unspecified

If signs of disturbance are present for more than a month but less than six months, the diagnosis of schizophreniform disorder is applied. Psychotic symptoms lasting less than a month may be diagnosed as brief psychotic disorder, and various conditions may be classed as psychotic disorder not otherwise specified. If the psychotic symptoms are the direct physiological result of a general medical condition or a substance, then the diagnosis is one of a psychosis secondary to that condition. Schizophrenia is not diagnosed if symptoms of pervasive developmental disorder are present unless prominent delusions or hallucinations are also present.

According to the DSM-5, to be diagnosed with schizophrenia, two diagnostic criteria have to be met over much of the time of a period of at least one month, with a significant impact on social or occupational functioning for at least six months. The person had to be suffering from

- Delusions
- hallucinations, or
- disorganized speech.

A second symptom could be negative symptoms, or severely disorganized or catatonic behavior.

Schizoaffective Disorder

Schizoaffective disorder is diagnosed if symptoms of mood disorder are substantially present alongside psychotic symptoms. Schizoaffective disorder may have etiologies which are different from schizophrenia, but to what extent is still unknown.

Differential diagnosis

- Individual symptoms by themselves or in varying combinations can also be present in other conditions. Some common examples are:
- Psychotic symptoms may be present in several other mental disorders, including bipolar disorder, borderline personality disorder, drug intoxication, and drug-induced psychosis.
- Delusions are also present in delusional disorder, and social withdrawal in social anxiety disorder, avoidant personality disorder and schizotypal personality disorder.
- Schizotypal personality disorder has symptoms that are similar but less severe than those of schizophrenia.
- Schizophrenia occurs along with obsessive-compulsive disorder (OCD) considerably more often than could be explained by chance, although it can be difficult to distinguish obsessions that occur in OCD from the delusions of schizophrenia.

- Benzodiazepine withdrawal can induce psychotic symptoms, which may mimic schizophrenia.
- In childhood various childhood fantasies can be experienced as very real. They are occasionally mistaken for psychotic symptoms.

Medical and Neurological Examination

Several conditions can cause psychotic or psychotic-like symptoms. These include the following:

- metabolic disturbance
- systemic infection
- syphilis
- AIDS dementia complex
- Epilepsy
- limbic encephalitis
- brain lesions

Stroke, multiple sclerosis, hyperthyroidism, hypothyroidism, and dementias such as Alzheimer's disease, Huntington's disease, frontotemporal dementia, and the Lewy body dementias may also be associated with schizophrenia-like psychotic symptoms.

It may be necessary to rule out a delirium, which is usually caused by an underlying medical condition and often manifests with

- acute onset and fluctuating level of consciousness, and
- visual hallucinations

Signs and symptoms

The symptoms of psychosis are the result of changes in how information is processed. Common is that the source of information is no longer interpreted correctly. For example, a thought turns into a voice which is heard from the outside. In this instance, the source is no longer identified correctly. It is not entirely clear why this happens. However, if one knows how this works, it is possible to integrate it and thereby reduce the fear of it and the extent to which hearing voices can interfere with everyday life. It also makes it possible to subject what one hears as voice to the same psychotherapeutic processes that would, for example, apply to ruminations or fearful content. Reality is subjective and awareness of a mental process can help to work with its outcomes. Communication-focused therapy (CFT) aims at awareness for internal and external communication patterns, which clinically also seems helpful in psychosis.(Haverkamp, 2012a, 2017b)

Symptom organization

Schizophrenia is often described in terms of positive and negative (or deficit) symptoms. Positive symptoms are those that most people do not normally experience but are present in people with schizophrenia. They can include delusions, disordered thoughts and speech, and tactile, auditory, visual, olfactory and gustatory hallucinations, typically regarded as manifestations of psychosis. Hallucinations are also typically related to the content of the delusional theme. Positive symptoms generally respond well to medication.

Negative symptoms are deficits of normal emotional responses or of other thought processes and are less responsive to medication. They commonly include flat expressions or little emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation. Negative symptoms appear to contribute more to poor quality of life, functional ability, and the burden on others than positive symptoms do. People with greater negative symptoms often have a history of poor adjustment before the onset of illness, and response to medication is often limited.

The validity of the positive and negative construct has been challenged by factor analysis studies. A cluster of symptoms around hallucination and a separate cluster for disorganization may be a more helpful categorization of the symptoms than combining them in the category of positive symptoms.

Some non-psychiatric symptoms, such as an increased need to drink fluids (polydipsia), can often be observed, while there is also an increased co-morbidity for irritable bowel syndrome, for example. Some of these non-psychiatric symptoms may be overlooked if not specifically asked for.

Cognitive Dysfunction

Deficits in cognitive abilities are widely recognized as a core feature of schizophrenia. The extent of the cognitive deficits someone experiences is a predictor of how functional they will be, the quality of occupational performance, and how successful they will be in maintaining treatment. The presence and degree of cognitive dysfunction in people with schizophrenia has been reported to be a better indicator of functionality than the presentation of positive or negative symptoms. The deficits impacting the cognitive function are found in a large number of areas, including

- working memory
- long-term memory
- verbal declarative memory
- semantic processing
- episodic memory
- attention
- learning (particularly verbal learning).

Self-instructional training can help patients with schizophrenia to alter their thinking, attention, and language behaviors by verbalizing tasks, engaging in cognitive rehearsal, giving self-instructions, giving coping statements to the self to handle failure, and providing self-reinforcement for success. This led to improvements in recall tasks, less nonsensical verbalizations, and greater satisfaction and quality of life, which in itself probably has a protective effect against psychotic symptoms by lowering fears and anxiety and allowing a better connection with the sense of self.

Verbal Memory

Deficits in verbal memory are common in schizophrenia. Verbal memory impairment in schizophrenia has been linked to a decreased ability to semantically encode. Healthy individuals usually remember words with positive connotations better than words with negative connotations. However, in those suffering from schizophrenia, both categories of words are remembered more or less equally. It could either be argued that the positive or negative value of the words is not recognized adequately or that the value no longer has as much an effect on the storage or access of the information. Thus, the impairment of memory can be linked to an impairment in the extraction of meaning or in how this information then affects the processing and storage of other information. If anhedonia is a state in which emotional signals are not processed and used as effectively, or differently from other people, it could be connected with alterations in storing and retrieving certain types of information, such as verbal messages or constructs.

Onset

The onset of the disorder is usually between ages 18 and 25 for men and between 25 and 35 for women, and in 40% of men and 23% of women diagnosed with schizophrenia, the condition manifested itself before the age of 19. A prodromal state can often be seen two to three years before the onset of the full set of symptoms.

Prodrome

The DSM-III-R published by the American Psychiatric Association in 1987 focuses mainly on observable behavioral changes in its description of the prodromal features of schizophrenia. It provides operationalized criteria of nine symptoms for the schizophrenic prodrome:

- Marked social isolation or withdrawal
- Marked impairment in role functioning
- Markedly peculiar behavior
- Marked impairment in personal hygiene and grooming
- Blunted or inappropriate affect

- Digressive, vague, overelaborate or circumstantial speech, or poverty of speech, or poverty of content of speech
- Odd beliefs or magical thinking
- Unusual perceptual experiences
- Marked lack of initiative, interests, or energy

This list of criteria has been dropped from the DSM-IV published in 1994. The ICD-10 published in the same year by the WHO acknowledges a prodrome as part of the schizophrenic syndrome, while prodromal symptoms are not included in its description of schizophrenia (Keith and Matthews 1991)

Hallucinations

As mentioned, a hallucination is an internal communication event which is perceived as an external one. A hallucination is defined as sensory perception in the absence of external stimuli. Hallucinations are different from illusions, or perceptual distortions which are the misperception of external stimuli. In an illusion an individual correctly identifies a communication event as external, however, it is distorted by internal communication events.

Hallucinations may occur in any of the senses and take on almost any form, which may include simple sensations (such as lights, colors, tastes, and smells) to experiences such as seeing and interacting with fully formed animals and people, hearing voices, and having complex tactile sensations. Hallucinations are generally characterized as being vivid, and uncontrollable.

Auditory hallucinations, particularly experiences of hearing voices, are the most common and often prominent feature of psychosis. They are a classical symptom of schizophrenia, although not everyone suffering from schizophrenia also has them. However, they may be underreported in schizophrenia, as rapping or knocking sounds at night or noise from installations are frequently auditory hallucinations that need to be actively asked for. In any case, it is important to remember that visual hallucinations, which are often popularly associated with schizophrenia, only occur in up to half of schizophrenic patients and are less common than auditory hallucinations, which studies give a prevalence in schizophrenia of significantly more than 50% and often over 90% and which can be overlooked if not asked for.

Brief hallucinations are not uncommon in those without any psychiatric disease. Causes or triggers include:

- Falling asleep (hypnagogic hallucination) and waking (hypnopompic hallucination)
- Bereavement, in which hallucinations of a deceased loved one are common
- Severe sleep deprivation
- Trauma

Voices

Auditory hallucinations are most commonly intelligible voices. They make be conversing or commenting about the patient. If they are imperative or commanding, they can elevate the risk that the patient may do something which he or she would not have done otherwise. This is another reason why it is important to educate patients on their condition and help them identify the type of communication patterns they are using and the source where the perceived information is coming from.

Since the sense of wholeness and connectedness of one's body can suffer in psychosis, hallucinations may also come from body parts. Auditory (extracampine) hallucinations may also originate from a particular body part, such as a tooth, which is not so rare. It may extend to a person hearing a whole symphony or a pop song coming from the body part, for example.

Delusions

Delusions are an interpretation of reality in a way which does not agree with the interpretations held by other people. Thus, delusions depend to a degree on the beliefs and views held in the community one lives in. The underlying process is again the interpretation of incoming information in a way which does not agree with the conclusions others draw from similar information. Since the sensory inputs, for example, are largely similar to those of others, the delusion must be a result of how the information is processed.

One explanation could be how existing information is weighed, making it possible that something highly unlikely is seen as the most likely interpretation of reality. At the same time, it seems to require that the focus is increased on an aspect of reality to the exclusion of others. Delusions are a heightened feeling of certainty about something which is most often not entirely unlikely, but very highly so.

Often, below the delusion are emotional signals which are, as in hallucinations, seen as happening in the outside world rather than on the inside. An emotional signal of anger may in this way lead to feeling persecuted by secret agents. While the secret agents themselves may not be angry, persecution is a close enough metaphorical expression for anger. As in the case of hallucinations, the information can thus not lead to the necessary changes that help the individual adapt better to the environment and have success in it. Rather than figuring out why one is angry and making changes in one's life, such as putting boundaries in place or changing jobs, one feels persecuted by secret agents, which only leads to further withdrawal.

The distinguishing feature between delusional thinking and full-blown delusions is the degree with which they impact functioning. Other delusions than the one mentioned include delusions of reference (beliefs that a particular stimulus has a special meaning that is directed at the holder of belief), grandiose delusions (delusions that a person has a special power or importance), thought broadcasting (the belief that one's thoughts are audible) and thought insertion (the belief that one's thoughts are not one's own). The DSM-5 characterizes certain delusions as 'bizarre' if they are clearly implausible or are incompatible within the cultural

context, while it is unlikely that any insight can be gained from the question whether one should label a delusion as 'bizarre' or not.

Historically, Karl Jaspers has classified psychotic delusions into primary and secondary types. Primary delusions are defined as arising suddenly and not being comprehensible in terms of normal mental processes, whereas secondary delusions are typically understood as being influenced by the person's background or current situation. However, in doing so he seemed to focus more on the external situation of a person, including the culture, rather than the internal signals, whether emotional or otherwise, that could also make a delusion 'comprehensible'.

Disorganization

While it is customary to talk about 'disorganized thinking' and 'disorganized speech' interchangeably, they are not the same. It is perfectly conceivable that a person has an internal world which seems quite clear and internally consistent to that person, but that the large differences between the internal world and the world of others makes meaningful communication near or fully impossible. When talking to someone who barely speaks one's language, the loss in understanding can cause significant stress and seemingly disorganized speech behavior. However, internally all along the world may be quite organized. Mistaking someone for an angry monster does not necessarily attest to a disorganized world, but it makes speaking to the angry drooling one eye monster quite a challenge, and the interaction is bound to be disorganized. The psychotic aspect is the existence of the monster, which causes any interaction to appear disorganized. This author thus believes there should be a clearer delineation between disorganized thinking, disorganized speech and cognitive impairment.

Disorganized speech

Disorganized speech is a common externally observable symptom in psychosis. Characteristics of disorganized speech include rapidly switching topics, called derailment or loose association; switching to topics that are unrelated, called tangential thinking; incomprehensible speech, called word salad or incoherence.

Disorganized motor behavior

Disorganized motor behavior includes repetitive, odd, or sometimes purposeless movement. One may add catatonia to disorganized motor behaviors, but it will be mentioned separately.

Self-Distortion

Distortions of self-experience such as feeling as if one's thoughts or feelings are not really one's own to believing thoughts are being inserted into one's mind, sometimes termed passivity phenomena, are also common. There is often an observable pattern of emotional

difficulty, for example lack of responsiveness. Impairment in social cognition is associated with schizophrenia, as are symptoms of paranoia. Social isolation commonly occurs. Difficulties in working and long-term memory, attention, executive functioning, and speed of processing also commonly occur. In one uncommon subtype, the person may be largely mute, remain motionless in bizarre postures, or exhibit purposeless agitation, all signs of catatonia. People with schizophrenia often find facial emotion perception to be difficult. It is unclear if the phenomenon called "thought blocking", where a talking person suddenly becomes silent for a few seconds to minutes, occurs in schizophrenia.

There is nearly universal acceptance that persons with schizophrenia often experience a profound disruption in their basic sense of self. The author has already described the sense of self as the ability of a person to experience the flows of information internally and externally with the outside world. (Haverkamp, 2010a, 2012b, 2017d)

Lysaker speculated that the subjective experience of personal incoherence in schizophrenia may reflect a collapse of the ability to maintain ongoing dialogue within the self, specifically arguing that as internal dialogues evaporate, self-experience and personal narrative can devolve into one of three forms: (a) a barren and empty self-organization; (b) internal cacophony; or (c) self-constructions dominated by rigid, non-evolving monologues. (Lysaker & Lysaker, 2002)

Catatonia

Catatonia describes a profoundly agitated state in which the experience of reality is generally considered impaired. There are two presentations of catatonia, one without movements and one with a lot of movement. Both, however, have in common that the individual is to an outside observer no longer interacting with the environment. That is, the information from the outside is no longer decoded or processed in a way which seem adaptive and helpful in getting the own needs met in the patient's outside reality.

- Stupor presents with waxy flexibility. Waxy flexibility is when someone physically moves part of a catatonic person's body and the person stays in the position even if it is bizarre. Patients may also switch their position suddenly and then remain in their new position for a length of time.
- Catatonic excitement is a state of constant purposeless agitation and excitation. Individuals in this state are extremely hyperactive, but without any discernible purpose within the outside world.
- Malignant catatonia is an acute onset of excitement, fever, autonomic instability, delirium and may be fatal.

The presence of hallucinations and delusions may be more obvious in catatonic excitement because the patient seems to react to an internal script of a different version of the world. In other words, some information about the internal representation of the world is still discernible by an outside observer. In the case of stupor, the patient has largely cut off any

communication with the outside world, which makes it difficult in this situation to gauge what he or she may be experiencing on the inside.

Catatonia is interesting from a communication viewpoint because it represents often a point at which the divergence between the internal representation of the outside world and the outside world as experienced by others is particularly great, and a disconnect may also partially serve to protect the patient from an experience of complete chaos.

Negative symptoms

While abnormal variations in the processing of information in psychosis can lead to positive symptoms in the form of hallucinations or delusions, they can also lead to negative symptoms, which mainly affect the use of emotional signals and a patient's communication with the world. Since the negative symptoms signify a lost function, there can be theoretically a large number of potential negative symptoms.

The ICD-10 provides the following areas of negative symptoms:

- marked apathy
- paucity of speech
- blunting or incongruity of emotional responses

The DSM-5 includes the following list:

- affective flattening
- alogia (poverty of speech)
- avolition (an inability to initiate and persist in goal-directed activities)

Anhedonia, the inability to find or derive pleasure from activities or relationships, and other symptoms have been described as associated symptoms in DSM-5.

From a communication perspective, it is important to note that our description of positive symptoms often entails a patient's perception of the world, or the consequences of that perception, while negative symptoms

Negative symptoms in schizophrenia may be classified as primary or secondary. Primary negative symptoms are thought to be intrinsic to schizophrenia, while secondary negative symptoms are caused by positive symptoms, depression, medication side-effects, social deprivation or substance abuse. Most of the research on secondary negative symptoms has aimed at ruling them out in order to isolate primary negative symptoms. However, secondary negative symptoms are common and can have a major impact on patient-relevant outcomes. Therefore, the assessment and treatment of secondary negative symptoms are clinically relevant. Furthermore, understanding the mechanisms underlying secondary negative symptoms can contribute to an integrated model of negative symptoms. In this review we provide an overview of concepts, evidence, assessment and treatment for the major causes

of secondary negative symptoms. We also summarize neuroimaging research relevant to secondary negative symptoms. We emphasize the relevance of recent developments in psychopathological assessment of negative symptoms, such as the distinction between amotivation and diminished expression, which have only rarely been applied in research on secondary negative symptoms. (Kirschner & Aleman, 2017)

Interest in the negative symptoms of schizophrenia has increased rapidly over the last several decades, paralleling a growing interest in functional, in addition to clinical, recovery, and evidence underscoring the importance negative symptoms play in the former. Efforts continue to better define and measure negative symptoms, distinguish their impact from that of other symptom domains, and establish effective treatments as well as trials to assess these. Multiple interventions have been the subject of investigation, to date, including numerous pharmacological strategies, brain stimulation, and non-somatic approaches. Level and quality of evidence vary considerably, but to this point, no specific treatment can be recommended. This is particularly problematic for individuals burdened with negative symptoms in the face of mild or absent positive symptoms. Presently, clinicians will sometimes turn to interventions that are seen as more “benign” and in line with routine clinical practice. Strategies include use of atypical antipsychotics, ensuring the lowest possible antipsychotic dose that maintains control of positive symptoms (this can involve a shift from antipsychotic polypharmacy to monotherapy), possibly an antidepressant trial (given diagnostic uncertainty and the frequent use of these drugs in schizophrenia), and non-somatic interventions (e.g., cognitive behavioral therapy, CBT). The array and diversity of strategies currently under investigation highlight the lack of evidence-based treatments and our limited understanding regarding negative symptoms underlying etiology and pathophysiology. Their onset, which can precede the first psychotic break, also means that treatments are delayed. From this perspective, identification of biomarkers and/or endophenotypes permitting earlier diagnosis and intervention may serve to improve treatment efficacy as well as outcomes. (Remington et al., 2016)

Causes

Psychosis has many different causes. These include mental illness, such as schizophrenia or bipolar disorder, sleep deprivation, some medical conditions, certain medications, and drugs such as alcohol or cannabis. One type, known as postpartum psychosis, can occur after giving birth. The neurotransmitter dopamine is believed to play a role. Acute psychosis is considered primary if it results from a psychiatric condition and secondary if it is caused by a medical condition. The diagnosis of a mental illness requires excluding other potential causes. Testing may be done to check for central nervous system diseases, toxins, or other health problems as a cause.

Stressful events or anything that interferes significantly with the normal workings of the central nervous system can potentially lead to psychotic or quasi-psychotic symptoms. Psychotic symptoms are thus not specific to a condition but can arise from several abnormalities in the information processing of the brain. As most psychiatric symptoms are a result of more global alterations in the information processing of the brain, psychotic symptoms are not an exception.

Genetic and environmental factors play a role in the development of schizophrenia. People with a family history of schizophrenia who have a transient psychosis have a 20–40% chance of being diagnosed with schizophrenia one year later.

The Dopamine Hypothesis

It is now known that dopamine is the primary neurotransmitter implicated in psychotic symptomology. Thus, blocking dopamine receptors (namely, the dopamine D2 receptors) and decreasing dopaminergic activity continues to be an effective but highly unrefined pharmacologic goal of antipsychotics. Recent pharmacological research suggests that the decrease in dopaminergic activity does not eradicate psychotic delusions or hallucinations, but rather attenuates the reward mechanisms involved in the development of delusional thinking; that is, connecting or finding meaningful relationships between unrelated stimuli or ideas.

Salience

The salience (also called saliency) of an item, be it an object, a person, a pixel, etc, is the state or quality by which it stands out relative to its neighbors. Saliency detection is considered to be a key attentional mechanism that facilitates learning and survival by enabling organisms to focus their limited perceptual and cognitive resources on the most pertinent subset of the available sensory data. Saliency typically arises from contrasts between items and their neighborhood.

A central role of dopamine is to mediate the “salience” of environmental events and internal representations. Kapur proposed that a dysregulated, hyperdopaminergic state, at a “brain” level of description and analysis, leads to an aberrant assignment of salience to the elements of one’s experience, at a “mind” level. Delusions are a cognitive effort by the patient to make sense of these aberrantly salient experiences, whereas hallucinations reflect a direct experience of the aberrant salience of internal representations. Antipsychotics “dampen the salience” of these abnormal experiences and by doing so permit the resolution of symptoms. (Kapur, 2003)

The anterior cingulate cortex and insula together constitute the salience network, an intrinsic large-scale network showing strong functional connectivity. The insular cortex is one of the brain regions that show consistent abnormalities in both structural and functional neuroimaging studies of schizophrenia. (Palaniyappan, 2012)

Schizophrenia is a highly disabling psychiatric disorder characterized by a range of positive “psychosis” symptoms. However, the neurobiology of psychosis and associated systems-level disruptions in the brain remain poorly understood. Here, we test an aberrant saliency model of psychosis, which posits that dysregulated dynamic cross-network interactions among the salience network (SN), central executive network, and default mode network contribute to

positive symptoms in patients with schizophrenia. In both cohorts, we found that dynamic SN-centered cross-network interactions were significantly reduced, less persistent, and more variable in patients with schizophrenia compared with control subjects. Multivariate classification analysis identified dynamic SN-centered cross-network interaction patterns as factors that distinguish patients from control subjects, with accuracies of 78% and 80% in the two cohorts, respectively. Crucially, in both cohorts, dynamic time-varying measures of SN-centered cross-network interactions were correlated with positive, but not negative, symptoms. (Supekar, Cai, Krishnadas, Palaniyappan, & Menon, 2019)

Brain Networks

Intrinsic functional brain networks are regions showing temporal coherence with one another. These INs are present in the context of a task (as opposed to an undirected task such as rest), albeit modulated to a degree both spatially and temporally. Prominent networks include the default mode, attentional fronto-parietal, executive control, bilateral temporal lobe, and motor networks.

Calhoun and colleagues tested for group differences in properties of INs including spatial maps, spectra, and functional network connectivity using independent component analysis. A small set of default mode, temporal lobe, and frontal networks with default mode regions appeared to play a key role in all comparisons. Bipolar subjects showed more prominent changes in ventromedial and prefrontal default mode regions whereas schizophrenia patients showed changes in posterior default mode regions. Anti-correlations between left parietal areas and dorsolateral prefrontal cortical areas were different in bipolar and schizophrenia patients and amplitude was significantly different from healthy controls in both patient groups. Patients exhibited similar frequency behavior across multiple networks with decreased low frequency power. (Calhoun et al., 2012)

Pathophysiology

Psychosis has been traditionally linked to the neurotransmitter dopamine. In particular, the dopamine hypothesis of psychosis has been influential and states that psychosis results from an overactivity of dopamine function in the brain, particularly in the mesolimbic pathway. The two major sources of evidence given to support this theory are that dopamine receptor D2 blocking drugs (i.e., antipsychotics) tend to reduce the intensity of psychotic symptoms, and that drugs that accentuate dopamine release, or inhibit its reuptake (such as amphetamines and cocaine) can trigger psychosis in some people (see stimulant psychosis).

Disruption in brain connectivity, driven primarily by a progressive reduction in dendritic spines on cortical pyramidal neurons, may represent a key triggering mechanism. The earliest disruptions appear to be in circuits involved in referencing experiences according to time,

place, and agency, which may result in a failure to recognize particular cognitions as self-generated or to constrain interpretations of the meaning of events based on prior experiences, providing the scaffolding for faulty reality testing. (Cannon, 2015)

Clinical high-risk individuals

Individuals at clinical high-risk (CHR) for psychosis are characterized by attenuated psychotic symptoms. Only a minority of CHR individuals convert to full-blown psychosis.

CHR individuals generally show an intermediate functional connectivity pattern between HCs and SZ patients but also have unique connectivity alterations. Du and colleagues found that ESZ patients showed more aberrant connectivities and greater alterations than CHR individuals. ESZ patients exhibited greater impairments than CHR individuals primarily in the cerebellum, frontal cortex, thalamus and temporal cortex, while CHR and ESZ populations shared common aberrances mainly in the supplementary motor area, parahippocampal gyrus and postcentral cortex. CHR-specific changes were also found in the connections between the superior frontal gyrus and calcarine cortex in the dominant state. (Du et al., 2018)

Microglial activity is elevated in patients with schizophrenia and in persons with subclinical symptoms who are at ultra high risk of psychosis and is related to at-risk symptom severity. These findings suggest that neuroinflammation is linked to the risk of psychosis and related disorders, as well as the expression of subclinical symptoms. (Bloomfield et al., 2016)

Immune Responses

Evidence from clinical studies analyzing patients' blood and cerebrospinal fluid samples, neuroimaging and post-mortem brain tissue suggests that aberrant immune responses may define schizophrenia illness' course through altered neuroplasticity representing abnormal aging processes. (De Picker, Morrens, Chance, & Boche, 2017)

Duration of untreated psychosis

Patients with first-episode psychosis experience psychotic symptoms for a mean of up to 2 years prior to initiation of treatment, and long duration of untreated psychosis (DUP) is associated with poor clinical outcomes. Meanwhile, evidence compiled from numerous studies suggests that longer DUP is not associated with structural brain abnormalities. Sarpal and colleagues found that longer DUP correlated with worse response to treatment as well as overall decreased functional connectivity between striatal nodes and specific regions within frontal and parietal cortices. Moreover, the relationship between DUP and treatment response was significantly mediated by corticostriatal connectivity. Their results indicate that variation in corticostriatal circuitry may play a role in the relationship between longer DUP

and worsened response to treatment. Future prospective studies are necessary to further characterize potential causal links between DUP, striatal circuitry and clinical outcomes. (Sarpal et al., 2017)

Low-Frequency Oscillations (LFOs)

Low-frequency oscillations (LFOs) of the blood oxygen level-dependent (BOLD) signal are gaining interest as potential biomarkers sensitive to neuropsychiatric pathology. Schizophrenia has been associated with alterations in intrinsic LFOs that covary with cognitive deficits and symptoms.

Findings indicate that LFO magnitude alterations relate to clinical symptoms and predate psychosis onset but are more pronounced in the early stages of schizophrenia. These differences were identified primarily in posterior cortex, including temporoparietal regions, extending into occipital and cerebellar lobes. Less LFO activity was related to greater symptom severity in both CHR and ESZ groups in several of these posterior cortical regions. (Fryer et al., 2016)

NMDA Receptors

An abnormally low levels of glutamate receptors found in the postmortem brains of those diagnosed with schizophrenia. Post-mortem studies demonstrate decreased expression of GAD67, GAT-1 and GABAA receptor subunits in the prefrontal cortex, although this appears to be restricted to certain neurons. In vivo imaging of GABAergic signaling appears to be moderately reduced, this may be dependent upon treatment and disease stage.

NMDA receptor dysfunction has been proposed as a mechanism in psychosis. This theory is reinforced by the fact that dissociative NMDA receptor antagonists such as ketamine, PCP and dextromethorphan (at large overdoses) induce a psychotic state. The symptoms of dissociative intoxication are also considered to mirror the symptoms of schizophrenia, including negative psychotic symptoms.

Reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function, and glutamate can affect dopamine function, both of which have been implicated in schizophrenia. However, positive symptoms fail to respond to glutamatergic medication.

The glutamate and dopamine hypotheses are leading theories of the pathoetiology of schizophrenia. Both were initially based on indirect evidence from pharmacological studies supported by post-mortem findings, but have since been substantially advanced by new lines of evidence from in vivo imaging studies. This review provides an update on the latest findings on dopamine and glutamate abnormalities in schizophrenia, focusing on in vivo neuroimaging studies in patients and clinical high-risk groups, and considers their implications for

understanding the biology and treatment of schizophrenia. These findings have refined both the dopamine and glutamate hypotheses, enabling greater anatomical and functional specificity, and have been complemented by preclinical evidence showing how the risk factors for schizophrenia impact on the dopamine and glutamate systems. The implications of this new evidence for understanding the development and treatment of schizophrenia are considered, and the gaps in current knowledge highlighted. Finally, the evidence for an integrated model of the interactions between the glutamate and dopamine systems is reviewed, and future directions discussed. (Howes, McCutcheon, & Stone, 2015)

Dopamine

The connection between dopamine and psychosis is generally believed complex. While dopamine receptor D2 suppresses adenylate cyclase activity, the D1 receptor increases it. If D2-blocking drugs are administered the blocked dopamine spills over to the D1 receptors. The increased adenylate cyclase activity affects genetic expression in the nerve cell, which takes time. Hence antipsychotic drugs take a week or two to reduce the symptoms of psychosis.

Particular attention has been paid to the function of dopamine in the mesolimbic pathway of the brain. This focus largely resulted from the accidental finding that phenothiazine drugs, which block dopamine function, could reduce psychotic symptoms. It is also supported by the fact that amphetamines, which trigger the release of dopamine, may exacerbate the psychotic symptoms in schizophrenia. The influential dopamine hypothesis of schizophrenia proposed that excessive activation of D2 receptors was the cause of (the positive symptoms of) schizophrenia. Although postulated for about 20 years based on the D2 blockade effect common to all antipsychotics, it was not until the mid-1990s that PET and SPET imaging studies provided supporting evidence. Dopamine D2/D3 receptors are elevated in schizophrenia, but the effect size is small, and only evident in medication naive schizophrenics. On the other hand, presynaptic dopamine metabolism and release is elevated despite no difference in dopamine transporter. The altered synthesis of dopamine in the nigrostriatal system have been confirmed in several human studies. Hypoactivity of dopamine D1 receptor activation in the prefrontal cortex has also been observed. The hyperactivity of D2 receptor stimulation and relative hypoactivity of D1 receptor stimulation is thought to contribute to cognitive dysfunction by disrupting signal to noise ratio in cortical microcircuits. The dopamine hypothesis is now thought to be simplistic, partly because newer antipsychotic medication (atypical antipsychotic medication) can be just as effective as older medication (typical antipsychotic medication), but also affects serotonin function and may have slightly less of a dopamine blocking effect.

Serotonin

Moreover, newer and equally effective antipsychotic drugs actually block slightly less dopamine in the brain than older drugs whilst also blocking 5-HT_{2A} receptors, suggesting the 'dopamine hypothesis' may be oversimplified. Soyka and colleagues found no evidence of

dopaminergic dysfunction in people with alcohol-induced psychosis and Zoldan et al reported moderately successful use of ondansetron, a 5-HT₃ receptor antagonist, in the treatment of levodopa psychosis in Parkinson's disease patients.

Reduced Grey Matter Volume

The anatomical level may be too coarse to get additional insight into the pathogenesis of psychosis. However, the selective variations in morphology and activity in certain areas of the brain may be able to point at underlying processes that could be affected in psychosis.

Schizophrenia is associated with subtle differences in brain structures, found in forty to fifty percent of cases, and in brain chemistry during acute psychotic states. Studies using neuropsychological tests and brain imaging technologies such as fMRI and PET to examine functional differences in brain activity have shown that differences seem to occur most commonly in the frontal lobes, hippocampus, and temporal lobes. Reductions in brain volume are most pronounced in grey matter structures, and correlate with duration of illness, although white matter abnormalities have also been found. A progressive increase in ventricular volume as well as a progressive reduction in grey matter in the frontal, parietal, and temporal lobes has also been observed. These differences have been linked to the neurocognitive deficits often associated with schizophrenia. Because neural circuits are altered, it has alternatively been suggested that schizophrenia could be thought of as a neurodevelopmental disorder with psychosis occurring as a possibly preventable late stage. There has been debate on whether treatment with antipsychotics can itself cause reduction of brain volume.

Both first episode psychosis, and high-risk status is associated with reductions in grey matter volume. Reductions in

- right middle temporal gyrus
- right superior temporal gyrus
- right parahippocampus
- right hippocampus
- right middle frontal gyrus
- left anterior cingulate cortex

have been observed in high risk populations. People with schizophrenia who are medication compliant have an association with enlarged lateral ventricles in the brain.

Hypoactivation

During attentional tasks, first episode psychosis is associated with hypoactivation in the right middle frontal gyrus, a region generally described as encompassing the dorsolateral prefrontal cortex (dlPFC). In congruence with studies on grey matter volume, hypoactivity in the right

insula, and right inferior parietal lobe is also reported. With the exceptions of reduced deactivation of the inferior frontal gyrus during cognitive tasks (i.e. hyperactivation), highly consistent and replicable hypoactivity in the right insula, dorsal anterior cingulate cortex, and precuneus, as well as hyperactivity in the right basal ganglia and thalamus is observed.

Decreased grey matter volume in conjunction with hypoactivity is observed in the dorsal ACC, right anterior/middle insula, and left middle insula. Decreased grey matter volume and hyperactivity is reported in the ventral anterior cingulate cortex, and more posterior regions of the insula.

Hallucinations

Studies during acute experience of hallucinations demonstrate increased activity in primary or secondary sensory cortices. As auditory hallucinations are most common in psychosis, most robust evidence exists for increased activity in the left middle temporal gyrus, left superior temporal gyrus, and left inferior frontal gyrus (i.e. Broca's area). Activity in the ventral striatum, hippocampus, and ACC are related to the lucidity of hallucinations, and indicate that activation or involvement of emotional circuitry are key to the impact of abnormal activity in sensory cortices. Together, these findings indicate abnormal processing of internally generated sensory experiences, coupled with abnormal emotional processing, results in hallucinations. One proposed model involves a failure of feedforward networks from sensory cortices to the inferior frontal cortex, which normally cancel out sensory cortex activity during internally generated speech. The resulting disruption in expected and perceived speech is thought to produce lucid hallucinatory experiences.

Delusions

The two-factor model of delusions posits that dysfunction in both belief formation systems and belief evaluation systems are necessary for delusions. Dysfunction in evaluations systems localized to the right lateral prefrontal cortex, regardless of delusion content, is supported by neuroimaging studies and is congruent with its role in conflict monitoring in healthy persons. Abnormal activation and reduced volume is seen in people with delusions, as well as in disorders associated with delusions such as frontotemporal dementia, psychosis and Lewy body dementia. Furthermore, lesions to this region are associated with "jumping to conclusions", damage to this region is associated with post-stroke delusions, and hypometabolism this region associated with caudate strokes presenting with delusions.

The aberrant salience model suggests that delusions are a result of people assigning excessive importance to irrelevant stimuli. In support of this hypothesis, regions normally associated with the salience network demonstrate reduced grey matter in people with delusions, and the neurotransmitter dopamine, which is widely implicated in salience processing, is also widely implicated in psychotic disorders.

Specific regions have been associated with specific types of delusions. The volume of the hippocampus and parahippocampus is related to paranoid delusions in Alzheimer's disease, and has been reported to be abnormal post mortem in one person with delusions. Capragas

delusions have been associated with occipito-temporal damage and may be related to failure to elicit normal emotions or memories in response to faces.

Negative symptoms

Psychosis is associated with ventral striatal hypoactivity during reward anticipation and feedback. Hypoactivity in the left ventral striatum is correlated with the severity of negative symptoms.

While anhedonia is a commonly reported symptom in psychosis, hedonic experiences are actually intact in most people with schizophrenia. The impairment that may present itself as anhedonia probably actually lies in the inability to identify goals, and to identify and engage in the behaviors necessary to achieve goals.

Studies support a deficiency in the neural representation of goals and goal directed behavior by demonstrating that receipt (not anticipation) of reward is associated with robust response in the ventral striatum.

- Reinforcement learning is intact when contingencies are implicit, but not when they require explicit processing.
- Reward prediction errors (during functional neuroimaging studies), particularly positive ones are abnormal.
- Anterior cingulate cortex (ACC) response, taken as an indicator of effort allocation, does not increase with reward or reward probability increase, and is associated with negative symptoms. The ACC is involved in certain higher-level functions, such as attention allocation, reward anticipation, decision-making, ethics and morality, impulse control (e.g. performance monitoring and error detection), and emotion. It probably also plays a role in autonomic functions.
- Deficits in dorsolateral prefrontal cortex (DLPFC) activity and failure to improve performance on cognitive tasks when offered monetary incentives are present. An important function of the DLPFC is the executive functions, such as working memory, cognitive flexibility, planning, inhibition, and abstract reasoning. The DLPFC is also the highest cortical area that is involved in motor planning, organization and regulation.
- Dopamine mediated functions are abnormal.

Genetics

Estimates of the heritability are that 80% of the individual differences in risk to schizophrenia is associated with genetics. The greatest single risk factor for developing schizophrenia is having a first-degree relative with the disease (risk is 6.5%), while more than 40% of monozygotic twins of those with schizophrenia are also affected. If one parent is affected the risk is about 13% and if both are affected the risk is nearly 50%.

Many genes are known to be involved in schizophrenia, each of small effect and unknown transmission and expression. The summation of these effect sizes into a polygenic risk score can explain at least 7% of the variability in liability for schizophrenia. Around 5% of cases of schizophrenia are understood to be at least partially attributable to rare copy number variants (CNVs), including 22q11, 1q21 and 16p11. These rare CNVs increase the risk of someone developing the disorder by up to a factor of twenty and are frequently comorbid with autism and intellectual disabilities. There is a genetic relation between the common variants which cause schizophrenia and bipolar disorder, an inverse genetic correlation with intelligence and no genetic correlation with immune disorders.

Zinc Finger Protein 804A gene

The Zinc Finger Protein 804A gene (ZNF804A) has been implicated in schizophrenia susceptibility by several genome-wide association studies. ZNF804A is brain expressed but of unknown function.

In the Irish samples, the ZNF804A genotype was associated with differences in episodic and working memory in patients but not in controls. These findings replicated in the same direction in the German samples. Furthermore, in both samples, when patients with a lower IQ were excluded, the association between ZNF804A and schizophrenia strengthened. In a disorder characterized by heterogeneity, a risk variant at ZNF804A seems to delineate a patient subgroup characterized by relatively spared cognitive ability. (Walters et al., 2010)

Immune Sensitivity

Increased immune sensitivity to gluten has been reported in schizophrenia.

Individuals with recent-onset psychosis and with multi-episode schizophrenia who have increased antibodies to gliadin may share some immunologic features of celiac disease, but their immune response to gliadin differs from that of celiac disease. In a study by Dickerson and colleagues, individuals with recent-onset psychosis had increased levels of IgG and IgA antibodies to gliadin compared with control subjects. Individuals with multi-episode schizophrenia also had significantly increased levels of IgG antibodies to gliadin. IgG antibodies to deamidated gliadin and IgA antibodies to tissue transglutaminase were not elevated in either psychiatric group, and fewer than 1% of individuals in each of the groups had levels of these antibodies predictive of celiac disease. (Dickerson et al., 2010)

Environment

Environmental factors associated with the development of schizophrenia include the living environment, drug use, and prenatal stressors.

Maternal stress has been associated with an increased risk of schizophrenia, possibly in association with reelin. Maternal Stress has been observed to lead to hypermethylation and therefore under-expression of reelin, which in animal models leads to reduction in GABAergic neurons, a common finding in schizophrenia. Maternal nutritional deficiencies, such as those observed during a famine, as well as maternal obesity have also been identified as possible risk factors for schizophrenia. Both maternal stress and infection have been demonstrated to alter fetal neurodevelopment through pro-inflammatory proteins such as IL-8 and TNF.

Patients with supportive parents are probably doing somewhat better than those with less supporting ones. Childhood trauma, death of a parent, and being bullied or abused increase the risk of psychosis. Living in an urban environment during childhood or as an adult has consistently been found to increase the risk of schizophrenia by a factor of two, even after taking into account drug use, ethnic group, and size of social group. Other factors that play an important role include social isolation and immigration related to social adversity, racial discrimination, family dysfunction, unemployment, and poor housing conditions. The important factor seems to be how a child or adolescent can build interactions with the world. Humans, and all living creatures in general, need meaningful information to succeed and prosper. Helpful interactions with others and a connectedness with oneself are the instrument to obtain this information. An interaction simply means there is a signal for information and a receiving of information. (Haverkamp, 2010a, 2018a) The process of acquiring information also helps the individual to distinguish between sources of information, and more globally whether the information originates on the inside or on the outside. Meaningful interactions could thus have a protective effect on the difficulties in identifying the sources of information in psychotic disorders.

Somatic Factors

Factors such as hypoxia and infection, or stress and malnutrition in the mother during fetal development, may result in a slight increase in the risk of schizophrenia later in life. Also, a subgroup of persons with schizophrenia present an immune response to gluten different from that found in people with celiac, with elevated levels of certain serum biomarkers of gluten sensitivity such as anti-gliadin IgG or anti-gliadin IgA antibodies. However, it is largely unclear how this may have an impact of the development of the condition.

Social Environment

The neurodevelopment hypothesis of schizophrenia has over the last three decades morphed into the developmental risk factor model of psychosis and integrated new evidence concerning dysregulated striatal dopamine as the final step on the pathway linking risk factors to psychotic symptoms. (Murray, Bhavsar, Tripoli, & Howes, 2017)

Social Isolation

According to stress-vulnerability models, social stressors contribute to the onset of schizophrenia. Stigma and discrimination associated with mental illness may be a stressor for young people at risk of psychosis even prior to illness onset. In a study by Rusch and colleagues, compared with participants who did not convert to schizophrenia, converters had

significantly more positive and negative symptoms and reported higher levels of stigma-related harm and stress at baseline. More perceived harm due to stigma at baseline predicted transition to schizophrenia after adjusting for age, gender, symptoms and functioning. Stigma stress may increase the risk of transition to schizophrenia. (Rüsch et al., 2015) However, stress vulnerability models often do not explain where the stress is coming from. Is social isolation causing stress or stress social isolation? The best explanation would probably be that they go hand in hand. Stress means communication with oneself and the environment does not bring the individual sufficiently close to getting the own needs, values and aspirations met. (Haverkamp, 2017c) Thus one experiences communication as less efficient and helpful, which makes the world as a whole less safe, predictable and comfortable. On the other hand, the experience of stress also changes how efficiently information from within and without can be selected, received and processed.

Animal studies have reported that long-term isolation may lead to reductions in volume of the total brain, hippocampus, or medial prefrontal cortex. Other animal studies reported that social defeat can reduce neurogenesis. (Selten, Booij, Buwalda, & Meyer-Lindenberg, 2017) One may speculate that since the brain needs a minimum input of changing information to equilibrate its own internal processes, if that 'food' is missing it can destabilize and 'atrophy'. However, the content of these information flows could conceivably also have an effect, such as information about relationships and interaction dynamics. After all, attachment is both, an information content, but maybe even more importantly, the expectation and experience of information flows. (Haverkamp, 2010a, 2018a)

Infections

People diagnosed with schizophrenia are about five to ten percent more likely to have been born in the colder months, which may be due to increased rates of viral exposures in utero. Other infections during pregnancy or around the time of birth including *Toxoplasma gondii* and Chlamydia, and some pathogens seropositivity are linked to an increase in risk. Viral infections of the brain during childhood are also linked to a risk of psychosis during adulthood.

Trauma

Traumatic life events have been linked with elevated risk in developing psychotic symptoms. Childhood trauma has specifically been shown to be a predictor of adolescent and adult psychosis. Approximately 65% of individuals with psychotic symptoms have experienced childhood trauma, such as physical or sexual abuse and physical or emotional neglect. Symptoms considered indicative of psychosis and schizophrenia, particularly hallucinations, are at least as strongly related to childhood abuse and neglect as many other mental health problems. Recent large-scale general population studies indicate the relationship is a causal one, with a dose-effect. (Read, Os, Morrison, & Ross, 2005)

There seems to be some correlation between the magnitude of accumulated traumata and the triggering of a psychotic episode. From an information perspective this makes sense. As there is information which tries to push the brain into a high level of change, such as a trauma, it could also stabilize information processing systems that help in such elemental mechanisms as distinguishing and selecting sources of information. (Haverkamp, 2012a) The objective in therapy is then to strengthen internal and external communication patterns that are adaptive and helpful to the individual patient, (Haverkamp, 2010b) which is one of the basic pillars of Communication-Focused Therapy® (Haverkamp, 2017b).

Medical conditions

Some medical conditions, which are known to cause psychotic and psychotic-like symptoms are as follows, although this list is by no means exhaustive:

- toxicity causing delirium and a ‘toxic psychosis’
- neurodevelopmental disorders
- chromosomal abnormalities
- neurodegenerative disorders
 - Alzheimer's disease
 - dementia with Lewy bodies
 - Parkinson's disease
- focal neurological disease, such as stroke, brain tumors, multiple sclerosis, and some forms of epilepsy
- malignancy (paraneoplastic syndromes)
- infectious and postinfectious syndromes, including infections causing delirium, viral encephalitis, HIV/AIDS, malaria, syphilis
- endocrine disorders, such as
 - hypothyroidism
 - hyperthyroidism
 - Cushing's syndrome
 - hypoparathyroidism and hyperparathyroidism
 - significant alterations in sex hormones
- giving birth can provoke psychosis (postpartum psychosis)
- genetic metabolic disorders
 - succinic semialdehyde dehydrogenase deficiency
 - porphyria
 - metachromatic leukodystrophy
- nutritional deficiency, such as vitamin B12 deficiency
- other acquired metabolic disorders, including
 - electrolyte disturbances such as hypocalcemia, hypernatremia, hyponatremia, hypokalemia, hypomagnesemia, hypermagnesemia, hypercalcemia, and hypophosphatemia
 - hypoglycemia
 - hypoxia
- failure of the liver or kidneys

- autoimmune and related disorders
 - systemic lupus erythematosus (lupus, SLE)
 - sarcoidosis
 - Hashimoto's encephalopathy
 - anti-NMDA-receptor encephalitis
 - non-celiac gluten sensitivity
- poisoning, by therapeutic drugs, recreational drugs, and a range of plants, fungi, metals, organic compounds, and a few animal toxins
- sleep disorders
 - narcolepsy (in which REM sleep intrudes into wakefulness)
- parasitic diseases
 - neurocysticercosis

As already mentioned, this list is far from exhaustive. Anything that significantly disturbs the information flows (and thus processing) in the brain, particularly the ones that provide information about information, can offset a psychosis if there is already a facilitating network constellation or biological predisposition for it, or both.

Psychoactive drugs

Psychotic and psychosis-like symptoms can occur either when being intoxicated or during withdrawal. The question of cause and effect is still being intensely debated, particularly in the case of cannabis. It may be that people who are predisposed to schizophrenia may be triggered by cannabis use, while cannabis is quite often used by the undiagnosed psychotic to self-medicate against the symptoms of psychosis, for example, to feel more 'relaxed' and 'distanced' from paranoid thoughts and delusions.

About half of those with schizophrenia use drugs or alcohol excessively. Amphetamine, cocaine, and to a lesser extent alcohol, can result in a transient stimulant psychosis or alcohol-related psychosis that presents very similarly to schizophrenia. Although it is not generally believed to be a cause of the illness, people with schizophrenia use nicotine at much higher rates than the general population.

Individuals who have a substance induced psychosis may have a greater awareness of their psychosis and a higher level of suicidal thinking compared to individuals who have a primary psychotic illness. However, this would seem to depend on several different factors, such as the pattern, frequency, dose and length of use, as well as environmental factors.

Substances that have been linked to psychotic symptoms include

- alcohol
- cannabis
- cocaine
- amphetamines
- cathinone

- psychedelic drugs (such as LSD and psilocybin)
- κ -opioid receptor agonists
- NMDA receptor antagonists, including phencyclidine and ketamine

Caffeine may worsen symptoms in those with schizophrenia and cause psychosis at very high doses in people without the condition.

Alcohol

Approximately three percent of people who are suffering from alcoholism experience psychosis during acute intoxication or withdrawal. The typical, occasionally observed chronic alcohol psychosis is probably due to a kindling mechanism. Alcohol causes alterations in membrane functioning and gene expression as well as thiamin and other deficiencies. Kindling refers to a neurological condition resulting from repeated withdrawal episodes from sedative-hypnotic drugs. An imbalance between inhibitory and excitatory amino acids and changes in monoamine release in the nervous system can lead to destabilization and neurotoxicity. The effects of an alcohol-related psychosis include an increased risk of depression and suicide as well as causing psychosocial impairments.

Cannabis

As mentioned above, there is a lively discussion about the cause and effect of psychosis in individuals using cannabis, particularly if used more regularly. Empirical data suggests that cannabinoids can produce a full range of transient schizophrenia-like positive, negative, and cognitive symptoms in some healthy individuals. Also, in individuals with an established psychotic disorder, cannabinoids can exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness. The mechanisms by which cannabinoids produce transient psychotic symptoms, while unclear may involve dopamine, GABA, and glutamate neurotransmission. Constellations of genes may predispose some individuals more than others to developing a psychotic episode when exposed to cannabis. However, only a very small proportion of the general population exposed to cannabinoids develop a psychotic illness. It is likely that cannabis exposure is a “component cause”, but is neither necessary nor sufficient to do so alone. (D’Souza, Sewell, & Ranganathan, 2009)

According to some studies, the more often cannabis is used the more likely a person is to develop a psychotic illness, with frequent use being correlated with twice the risk of psychosis and schizophrenia. However, it is difficult to distinguish this from a use of cannabis as self-medication in patients who experience early and incomplete symptoms of psychosis. As the progression of psychosis can vary among individuals, and in some cases linger for many years, or even indefinitely, in a partial clinical picture, there is no way of saying for sure what would have happened if the patient would not have used cannabis.

While cannabis use is accepted as a contributory cause of schizophrenia by some, it remains controversial, with pre-existing vulnerability to psychosis emerging as the key factor that influences the link between cannabis use and psychosis. Some studies indicate that the effects of two active compounds in cannabis, tetrahydrocannabinol (THC) and cannabidiol (CBD), have opposite effects with respect to psychosis. While THC can induce psychotic symptoms in healthy individuals, CBD may reduce the symptoms caused by cannabis.

Cannabis use has increased dramatically over the past few decades whereas the rate of psychosis has not increased, which may suggest that cannabis use may hasten the onset of psychosis in those who already have a predisposition to psychosis. High-potency cannabis use indeed seems to accelerate the onset of psychosis in predisposed patients. On the other hand, the use of cannabis in self-medicate against the (prodromal) symptoms of a psychosis may also underline the potential calming effect of cannabis in some. Still, it would seem safer to avoid cannabis and use proper antipsychotic medication to the quality of life and reduce the huge impairments in a patient's daily life which are caused by the condition.

Methamphetamine

Methamphetamine induces a psychosis in about a quarter to half of all heavy users. Some develop a long-lasting psychosis that can persist for longer than six months. Those who have had a short-lived psychosis from methamphetamine can have a relapse of the methamphetamine psychosis years later after a stress event such as severe insomnia or a period of heavy alcohol abuse despite not relapsing back to methamphetamine. Acute psychosis induced by amphetamines seems to have a faster recovery and appears to resolve more completely compared to schizophrenic psychosis.

The increased vulnerability for acute amphetamine induced psychosis seen among those with schizophrenia, schizotypal personality and, to a certain degree other psychiatric disorders, is also shared by non-psychiatric individuals who previously have experienced amphetamine-induced psychosis. Schizophrenia spectrum disorder and amphetamine-induced psychosis are likely to have several common susceptibility gene. These genes probably lower the threshold for becoming psychotic and increase the risk for a poorer clinical course of the disease. (Bramness et al., 2012)

Medication

Several forms of medication may induce psychotic or psychosis-like side effects, including depersonalization, derealization and psychotic symptoms like hallucinations. Drugs that can induce psychosis experimentally or in a significant proportion of people include amphetamine and other sympathomimetics, dopamine agonists, ketamine, corticosteroids (often with mood changes in addition), and some anticonvulsants such as vigabatrin. Stimulants may cause this condition as well, such as lisdexamfetamine.

Diagnosis

To make a diagnosis of a mental illness in someone with psychosis other potential causes must be excluded. An initial assessment includes a comprehensive history and physical examination. Tests may be done to exclude substance use, medication, toxins, surgical complications, or other medical illnesses.

Delirium should be ruled out, which can be distinguished by visual hallucinations, acute onset and fluctuating level of consciousness, indicating other underlying factors, including medical illnesses. Excluding medical illnesses associated with psychosis is performed by using blood tests to measure:

- Thyroid-stimulating hormone to exclude hypo- or hyperthyroidism,
- Basic electrolytes and serum calcium to rule out a metabolic disturbance,
- Full blood count including ESR to rule out a systemic infection or chronic disease, and
- Serology to exclude syphilis or HIV infection.

Other investigations include:

- EEG to exclude epilepsy, and an
- MRI or CT scan of the head to exclude brain lesions.

Because psychosis may be precipitated or exacerbated by common classes of medications, medication-induced psychosis should be ruled out, particularly for first-episode psychosis. Both substance- and medication-induced psychosis can be excluded to a high level of certainty, using toxicology screening.

Because some dietary supplements may also induce psychosis or mania, but cannot be ruled out with laboratory tests, a psychotic individual's family, partner, or friends should be asked whether the patient is currently taking any dietary supplements.

Common mistakes made when diagnosing people who are psychotic include:

- Not properly excluding delirium,
- Not appreciating medical abnormalities (e.g., vital signs),
- Not obtaining a medical history and family history,
- Indiscriminate screening without an organizing framework,
- Missing a toxic psychosis by not screening for substances and medications,
- Not asking family or others about dietary supplements,
- Premature diagnostic closure, and
- Not revisiting or questioning the initial diagnostic impression of primary psychiatric disorder.

Only after relevant and known causes of psychosis are excluded, a mental health clinician may make a psychiatric differential diagnosis using a person's family history, incorporating information from the person with psychosis, and information from family, friends, or significant others.

Prevention

There is some evidence that early intervention in those with a psychotic episode may improve short-term outcomes, but there is little evidence for a long-term benefit. Cognitive behavioral therapy (CBT) may reduce the risk of becoming psychotic in those at high risk. An intensive multi-disciplinary approach is usually preferred, which may not prevent a full psychotic episode, but it can help to prevent the long-term impairments of a chronic illness. Negative symptoms in particular, e.g. social withdrawal, reduced initiative, anhedonia and affective flattening, are notoriously difficult to treat. (Kirschner & Aleman, 2017)

Communication-Focused Therapy[®], as developed by the author, focuses on the internal and external communication patterns and information flows. Since there are variations in how information is processed and communicated in psychotic patients, it has been reported that it has been helpful in individual patients (Haverkamp, 2012a, 2017b).

While the evidence for the effectiveness of early interventions to prevent psychosis appears largely inconclusive, drug induced psychosis can be avoided. This approach uses tools largely from the field of addiction prevention and treatment.

Treatment

Long-term hospitalization has become uncommon due to the advances in pharmacological treatment from the 1950s and onwards. Medication should always be combined with psychotherapy, even if the latter is at longer intervals and mainly of a supportive nature. Community support services including drop-in centers, visits by members of a community mental health team, supported employment and support groups are common. Some evidence indicates that regular exercise has a positive effect on the physical and mental health of those with schizophrenia. Early treatment is crucial. With every relapse there seems to be a larger risk that some symptoms may become chronic and irreversible, particularly cognitive impairments, anhedonia, indifference, apathy and other negative symptoms.

Medication is often cited as the first treatment instrument, followed by psychotherapy and social support. While medication can indeed often lead to a rapid decrease in symptoms, psychotherapy is frequently underutilized, probably due to a lack in resources, but also due to a lack in understanding what psychotherapy can accomplish. A good treatment plan would include all three pillars, the biological, the psychological and the social. Since all three have an effect on how the patient utilizes and communicates meaningful information and are

inseparable in practice, if one of these three treatment areas is neglected, the patient may feel the additional stress of coping with it alone, which can then compromise the effectiveness of working with the other two.

On the psychotherapeutic side, early work with psychotic and schizophrenic patients showed that it could have an effect on symptoms, at a time when most medical quarters were openly thinking of and practicing psychosurgery. Freud's former student Wilhelm Reich explored independent insights into the physical effects of neurotic and traumatic upbringing and published his holistic psychoanalytic treatment with a schizophrenic. With his incorporation of breathwork and insight with the patient, a young woman, she achieved adequate self-management skills to end the therapy.

Major psychosocial approaches concern social skills training, cognitive behavior therapy for psychosis, cognitive remediation and family intervention. Some positive findings have been reported, with the most robust improvements observed for social skills training. (Kirschner & Aleman, 2017)

Some small studies have suggested improvement of negative symptoms after non-invasive electromagnetic neurostimulation, but this has only been partly replicated and it is still unclear whether these are robust improvements. (Kirschner & Aleman, 2017)

Medication

The first-line psychiatric treatment for schizophrenia is antipsychotic medication, which can reduce the positive symptoms often within days in an acute episode. With regard to pharmacological interventions, antipsychotics have been shown to improve negative symptoms, but this seems to be limited to secondary negative symptoms in acute patients. It has also been suggested that antipsychotics may aggravate negative symptoms. (Kirschner & Aleman, 2017)

Treatment was revolutionized in the mid-1950s with the development and introduction of chlorpromazine. Haloperidol has become a mainstay in the pharmacological treatment of acute episodes of schizophrenia. For the longer-term treatment, mainly atypical or second-generation antipsychotics are used, such as olanzapine, quetiapine, aripiprazole, risperidone, amisulpride and others. Medication has made most cases of schizophrenia quite manageable, allowing patients to pursue their everyday jobs and raise a family. In about half of patients there is a good response and in another third a partial response. Their effect on negative symptoms and cognitive impairments is, however, generally smaller than on the positive (productive) symptoms of psychosis. Clozapine is an effective treatment for those who respond poorly to other drugs ("treatment-resistant" or "refractory" schizophrenia), but it has the potentially serious, and even lethal, side effect of agranulocytosis (lowered white blood cell count) in a small fraction of the patients.

Patients on typical antipsychotics tend to have a higher rate of extrapyramidal side effects while some atypical antipsychotics are associated with considerable weight gain, diabetes and

risk of metabolic syndrome. Olanzapine probably carries the highest risk, while risperidone and quetiapine are also associated with weight gain. Risperidone has a similar rate of extrapyramidal symptoms to haloperidol, although probably mostly in a higher dose range. Olanzapine, and to some degree quetiapine and possibly risperidone, have the added benefit of being sleep inducing.

Potential side effects of all antipsychotics, possibly with the exception of clozapine and arguably to a lesser degree in the second-generation antipsychotics, include irreversible Parkinsonian symptoms such as tardive dyskinesia.

Typical vs Atypical Antipsychotics

Second generation, or atypical, antipsychotics are usually considered to lead to less, and particularly less severe side effects. While older antipsychotics, like haloperidol, are often used in acute psychotic states, over time they may be more prone to lead to such irreversible side effects as tardive dyskinesia, which belongs to the group of extrapyramidal side effects. This is probably the reason one sees less involuntary facial movements, including the movements of the tongue, in a younger population suffering from psychosis, while it is unclear whether atypical antipsychotics truly lead to lower rates of tardive dyskinesia. All the newer antipsychotics, maybe excepting clozapine, can also lead to extrapyramidal side effects, albeit probably less frequently.

The frequent main problem with second generation antipsychotics is the greater risk of a metabolic syndrome. This is probably related to the greater affinity for serotonin receptors, which at the same time, together with the different affinities for dopamine receptor subclasses, may also lead to the lower rates of extrapyramidal side effects. Atypical antipsychotics, particularly olanzapine, are associated with considerable weight gain, diabetes and risk of metabolic syndrome. Risperidone and quetiapine can also lead to weight gain, aripiprazole due to its different pattern of receptor affinities probably considerably less so.

For people who are unwilling or unable to take medication regularly, long-acting depot preparations of antipsychotics may be used to achieve control. They reduce the risk of relapse to a greater degree than oral medications. However, they should only be used if the patient has been on the oral preparation for a sufficient length of time and without side effects that could be a reason for concern, because once the depot has been administered it stays in the body and gives off medication for weeks or months.

Discontinuing Medication

Antipsychotic medication should be reduced carefully, and then only gradually, unless side effects require an immediate stop or switch to another medication. Aside from a metabolic syndrome and other changes of blood parameters, one always has to keep in mind the risk from a relapse to the individual and his or her environment. It is generally understood a higher

the number of psychotic episodes can lead to greater chronicity with more permanent and potentially irreversible negative side effects, such as cognitive impairments, lack of motivation and emotional flattening.(Haverkamp, 2013) The American Psychiatric Association thus suggests considering stopping antipsychotics in some people if there are no symptoms for more than a year.

Psychosocial Therapies

A number of psychosocial interventions may be useful in the treatment of schizophrenia including:

- family therapy
- assertive community treatment
- supported employment
- cognitive remediation
- skills training
- token economic interventions
- psychosocial interventions for substance use and weight management

Psychotherapy

There are many approaches for schizophrenia from a psychotherapeutic perspective. Unfortunately, due to lack of resources this important long-term treatment is often relegated to a lesser importance, if it is initiated at all. Standardized treatment guidelines recommend psychotherapy (National Institute for Clinical Excellence [NICE], 2014). Meta-analyses show positive effects both on symptoms and recovery (Lysaker et al., 2010; Jones et al., 2012; Okuzawa et al., 2014), especially for therapies >20 sessions (Sarin et al., 2011).

Although cognitive behavior therapy shows significant effects for negative symptoms as a secondary outcome measure, there is a lack of data to allow for definite conclusions of its effectiveness for patients with predominant negative symptoms. (Kirschner & Aleman, 2017) Psychological treatments such as acceptance and commitment therapy (ACT) are possibly useful in the treatment of psychosis, helping people to focus more on what they can do in terms of valued life directions despite challenging symptomology.

Many psychological mechanisms have been implicated in the development and maintenance of schizophrenia. Cognitive biases have been identified in those with the diagnosis or those at risk, especially when under stress or in confusing situations. Some cognitive features may reflect global neurocognitive deficits such as memory loss; others may be related to particular issues and experiences.

Despite a demonstrated appearance of blunted affect, recent findings indicate that many people diagnosed with schizophrenia are emotionally responsive, particularly to stressful or negative stimuli, and that such sensitivity may cause vulnerability to symptoms or to the disorder. Some evidence suggests that the content of delusional beliefs and psychotic experiences can reflect emotional causes of the disorder, and that how a person interprets such experiences can influence symptomatology. The use of "safety behaviors" (acts such as gestures or the use of words in specific contexts) to avoid or neutralize imagined threats may actually contribute to the chronicity of delusions. Further evidence for the role of psychological mechanisms comes from the effects of psychotherapies on symptoms of schizophrenia.

CBT and Psychodynamic Psychotherapy

Even with adequate medication management and adherence, at least half of patients continue to suffer from distressing psychotic symptoms (Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004). However, data from the AESOP-10 multicenter study, a 10-year follow-up of a large epidemiologically characterized cohort of 557 people with first-episode psychosis suggests that remission and recovery are more common than previously believed. (Revier et al., 2015) There is a great deal of evidence now supporting the use of CBT for psychosis (CBTp). It is also recommended by the National Treatment Guidelines in both the U.K. and the U.S. (Naeem et al., 2016)

This points to the importance of psychotherapy, which can be a highly selective way to bring about change, both psychological and neurobiological. (Haverkamp, 2017a, 2018c) The majority of research is on cognitive behavioral therapy (CBT) (Burns et al., 2014; Hutton and Taylor, 2014). However, meta-analyses have found no clear evidence that CBT is superior to other psychotherapeutic approaches (Tolin, 2010; Jones et al., 2012). Since the techniques among the studied therapeutic approaches varied significantly, it may be what all the communication-oriented therapies have in common, communication, which helps achieve results. Communication-Focused Therapy (CFT) as a psychotherapeutic model which works directly with communication mechanisms (Haverkamp, 2010b, 2018b) will be outlined below. It must be added, however, that even with the obvious benefit millions of patients derive from psychotherapy every year, the factors driving psychotherapeutic change in psychosis remain understudied (Stafford et al., 2013).

Mentalization-based psychodynamic psychotherapy is another psychotherapeutic approach, which targets disturbances of awareness of the self and others in patients with psychotic-spectrum disorders. Mentalization-based psychotherapy may offer a useful adjunct to antipsychotic medication and psychosocial evidence-based treatments in the care of individuals in the early phase of psychotic disorders.

The findings from the Danish schizophrenia project (DNS) support the use of psychodynamic psychotherapy for psychosis in patients with a first-episode schizophrenia spectrum disorder. The study was designed as a prospective, comparative, longitudinal multi-site investigation of consecutively referred patients who were included during two years. The patients in the

treatment group underwent manualized individual supportive psychodynamic psychotherapy (SPP) in addition to treatment as usual. The intervention group improved significantly on measures of both PANSS and GAF scores, with large effect sizes at two years follow-up after inclusion. Further, improvement on GAF function ($p = 0.000$) and GAF symptom ($p = 0.010$) significantly favored SPP in combination with treatment as usual over treatment as usual alone.

In a meta-analysis Naeem and colleagues found a moderate effect size for brief CBTp compared with treatment as usual and a small effect size for brief CBTp compared with other treatments. The effect size for the negative symptoms was larger than that for the positive symptoms. Among the positive symptoms the highest effect size was found in favor of delusions. These effect sizes were maintained at follow-up. (Naeem et al., 2016)

Cognitive Remediation

Cognitive remediation (CR) is a treatment targeting cognitive difficulties in people with schizophrenia. Recent research suggested that CR may also have a positive effect on negative symptoms. (Cella, Preti, Edwards, Dow, & Wykes, 2017) A meta-analysis by Cella and colleagues estimated the effect of CR on negative symptoms. Although negative symptoms have not been considered a primary target for CR, this intervention can have small to moderate beneficial effects on this symptom cluster. (Cella et al., 2017)

Computer-Mediated Therapy

Cognitive deficits have been linked to a poorer outcome and hence specific cognitive remediation therapies have been proposed. Their effectiveness is nowadays approved and neurobiological correlates have been reconfirmed by brain imaging studies. (Suenderhauf, Walter, Lenz, Lang, & Borgwardt, 2016)

Recent MRI work showed that commercial video games modified similar brain areas as these specialized training programs. If gray matter increases and functional brain modulations would translate in better cognitive and every day functioning, commercial video game training could be an enjoyable and economically interesting treatment option for patients with neuropsychiatric disorders. (Suenderhauf et al., 2016)

Theory of Mind

Theory of mind (ToM) deficit is a well-established feature of schizophrenia and has been suggested as a vulnerability marker of this disorder. In a meta-analysis by Bora and Pantelis, ToM was substantially impaired in first-episode psychosis and this deficit was comparable to findings in chronic patients. ToM was also impaired in unaffected relatives and UHR subjects

and performances of these groups were intermediate between FES and healthy controls. Severity of ToM deficits in unaffected relatives and UHR subjects was similar to other cognitive deficits observed in these groups. (Bora & Pantelis, 2013)

Communication-Focused Therapy® (CFT)

Communication-Focused Therapy (CFT) was developed by the author to focus more specifically on the communication process between patient and therapist and use it to help the patient acquire more insight and better skills in it. The central piece is that the sending and receiving of meaningful messages is at the heart of any process leading to changes in thoughts or external situations. CBT, psychodynamic psychotherapy and IPT help because they define a format in which communication processes take place that can bring about change without focusing on them. CFT tries to be more efficient in a therapeutic sense by focusing on them more directly.

At the start when treating psychosis, it may appear difficult to engage in a constructive communication process. However, organisms in general tend to react to information if it reaches them somehow. Even in states which seem very closed off, the brain still receives and processes information streaming in from the external world. Persistence, and in many cases antipsychotic medication as a supportive tool, often help to get the patient to a point where they get used to the constant messages, fears decline, and it becomes easier to initiate a response. It is important to remember that it is almost impossible under normal circumstances not to interact with someone who repeatedly sends messages at oneself.

Psychosis means losing touch with reality in one's perception of what is real. It is thus a failure in meaningful communication. Medication is often the first-line treatment, and many psychotherapy schools are reluctant to work with people suffering from psychotic symptoms. However, underlying most psychotherapies is the belief in the effectiveness of interpersonal communication, the 'talk therapy'. Since in psychosis there are patterns of communication with oneself and others that are causing symptoms and are not helpful to the individual, using therapy to change them can be very helpful in the treatment and management of psychosis.

Schizophrenia research has been in a deadlock for many decades. Despite important advances in clinical treatment, there are still major concerns regarding long-term psychosocial reintegration and disease management, biological heterogeneity, unsatisfactory predictors of individual course and treatment strategies, and a confusing variety of controversial theories about its etiology and pathophysiological mechanisms. In the present perspective on schizophrenia research, we first discuss a methodological pitfall in contemporary schizophrenia research inherent in the attempt to link mental phenomena with the brain: we claim that the time-honored phenomenological method of defining mental symptoms should not be contaminated with the naturalistic approach of modern neuroscience. We then describe our Systems Neuroscience of Psychosis (SyNoPsis) project, which aims to overcome this intrinsic problem of psychiatric research. Considering schizophrenia primarily as a disorder of interindividual communication, we developed a neurobiologically informed semiotics of psychotic disorders, as well as an operational clinical rating scale. The novel

psychopathology allows disentangling the clinical manifestations of schizophrenia into behavioral domains matching the functions of three well-described higher-order corticobasal brain systems involved in interindividual human communication, namely, the limbic, associative, and motor loops, including their corticocortical sensorimotor connections. The results of several empirical studies support the hypothesis that the proposed three-dimensional symptom structure, segregated into the affective, the language, and the motor domain, can be specifically mapped onto structural and functional abnormalities of the respective brain systems. New pathophysiological hypotheses derived from this brain system-oriented approach have helped to develop and improve novel treatment strategies with noninvasive brain stimulation and practicable clinical parameters. In clinical practice, the novel psychopathology allows confining the communication deficits of the individual patient, shifting attention from the symptoms to the intact resources. We have studied this approach and observed important advantages for therapeutic alliances, personalized treatment, and de-escalation strategies. Future studies will further conjoin clinical definitions of psychotic symptoms with brain structures and functions, and disentangle structural and functional deficit patterns within these systems to identify neurobiologically distinct subsyndromes. Neurobiologically homogeneous patient groups may provide new momentum for treatment research. Finally, lessons learned from schizophrenia research may contribute to developing a comprehensive perspective on human experience and behavior that integrates methodologically distinct, but internally consistent, insights from humanities and neuroscience. (Strik, Stegmayer, Walther, & Dierks, 2017)

Reality

When people speak of reality, they really often mean shared reality. Shared reality is the perceptions the majority of people have. It does not necessarily mean that this is the ‘true’ reality, but it is how the majority of people see the world.

The shared reality may not necessarily be the ‘best’ reality. Someone could be happy interpreting the world in a different way. Part of the shared reality is due to a shared anatomy and physiology; another part is due to the exchange of information between people. Psychosis affects how information is processed. Besides medication, helping people to have a different perspective on the flows of information and process them differently is an important way to treat psychosis. By helping patients to receive more information and be more perceptive to reality, they can also ‘build’ a reality which causes less suffering and is better suited to have their needs and wants met.

An important feature of reality is where one perceives that information is coming from. If one hears voices, internal thoughts are misinterpreted as external voices, or if one feels pursued by a secret agent, an aggressive emotion, for example, leads to an aggressive person in the outside world. Better insight into communication and learning communication skills can also help the patient to better localize sources of messages and build a more stable view and sense of reality.

Learning through Communication

Learning to identify better the sources of information, inside one's own body and in the outside world, can help to attach the correct meaning to a sensation or a voice one hears. This can be trained in the communication space of a psychotherapeutic setting. Practicing communication and reflecting on it helps the patient to develop greater insight and sharpen his or her communication skills.

Learning about communication usually includes a theoretical psychoeducational component and a practical component. Engaging in communication can be important to increase one's confidence and skills in the process. At the same time, better proficiency in communication also makes any other learning processes easier.

Resources

Patients suffering from psychosis often lose a sense of their own resources because the self becomes fleeting and less accessible. In the therapeutic interaction, through the communication process a more stable distinction between the inside and outside worlds can be established, which strengthens the sense of self, and thus makes the own resources more accessible.

Using communication more optimally can, for example, compensate for various cognitive impairments which are often a part of psychosis. Certain strengths can be used better if the communication with oneself and the world around improves. Resources can also be easier felt and relied upon if one communicates better with oneself, which may include being better at identifying where information comes from, especially if it represents an emotion, what it means, and how one can react to it.

Psychosis

Psychosis is an abnormal condition of the mind that involves a loss of contact with reality. People experiencing psychosis may exhibit personality changes and thought disorder. Depending on its severity, this may be accompanied by unusual or bizarre behavior, as well as difficulty with social interaction and impairment in carrying out daily life activities. Generally, psychosis involves noticeable deficits in normal behavior and thought (negative symptoms) and often various types of hallucinations or delusional beliefs, particularly with regard to the relation between self and others as in grandiosity or paranoia (positive symptoms).

Unfortunately, psychosis as a diagnostic term is often used after other reasons have been excluded. It may therefore be more illuminating to think of psychosis as a mental process involving changes in how information flows and how these flows are interpreted, which can occur in various psychiatric conditions.

Misinterpretation of Sources of Information

As the information can no longer be correctly attributed to an outside or an inside source, the individual experiences own thoughts coming from outside in the form of voices or people on the outside as part of internal mental processes and might experience this as people having influence on the own thoughts. From the differently perceived localization of perceptions and messages a different reality is constructed. Since the pieces often do not integrate as well into it as in the shared reality, gaps can result, which then lead to fears, often of an intense and existential nature.

Misinterpretation of Messages

A misinterpretation of messages is different from a misinterpretation of the sources of information, but they often seem to go hand in hand in psychosis. The conviction that someone is pursued by a neighbor, who is a spy, can be a misinterpretation of an emotion towards this neighbor as a (real) outside event, while a smile from the neighbor in the hallway can be interpreted as her satisfaction about having made a plan to harm the patient, which would be a misinterpretation of her original message of saying 'Hi'.

A misinterpretation of messages usually occurs with respect to the universe of the patient, emotionally and perceptually. When focusing on the communication in therapy, it is therefore important to first get a sense for the universe the patient finds himself or herself in, both perceptually and emotionally. This information allows the therapist to build a better rapport with the patient, since the messages from the therapist will be interpreted by the patient within the context of this universe.

A Diversity of Symptoms

A host of symptoms can be deduced from the underlying mechanism. Psychosis is often used descriptive term for the hallucinations, delusions and impaired insight that may occur as part of a psychiatric disorder. More correct would be to use it to describe the alterations in information recognition and processing. Some symptoms can be due to a misinterpretation in the source of the information, or as a misinterpretation of one's own position relative to the source of information, while others are clearly due to a misinterpretation of the messages.

Communication is Life

We engage constantly in communication. The cells in our bodies do so with each other using electrical current, molecules, vibrations or even electromagnetic waves. People communicate with each other also through a multitude of channels, which may on several technologies and intermediaries. It does not have to be an email. Spoken communication requires multiple signal translations from electrical and chemical transmission in the nervous system to mechanical transmission as the muscles and the air stream determine the motions of the vocal chords and then as sound waves travelling through the air, followed by various translations on the receiving end. At each end, in the sender and in the receiver, there is also a processing of information which relies on the highly complex networks of the nervous system. Communication, in short, happens everywhere all the time. It is an integral part of life. Certain communication patterns can, however, also contribute to experiencing anxiety and panic attacks.

Autoregulation

Communication is an autoregulatory mechanism. It ensures that living organisms, including people, can adapt to their environment and live a life according to their interests, desires, values, and aspirations. This does not only require communicating with a salesperson, writing an exam paper or watching a movie, but also finding out more about oneself, psychologically and physically. Whether measuring one's strength at the gym or engaging in self-talk, this self-exploration requires flows of relevant and meaningful information. Communication allows us to have a sense of self and a grasp of who we are and what we need and want in the world, but it has to be learned similar to our communication with other people.

Understanding Psychosis

In psychosis the internal and external worlds cannot be distinguished as accurately anymore. They seem to blend into each other. This can cause various symptoms that are then summarized as 'psychotic'. However, each symptom should make sense in the context of the patient's communication patterns as well as the life experiences and emotions the patient faces, which influence the content of the psychosis. Having an understanding for what is happening, is important because it also helps make the patient feel more secure.

Another feature of psychosis is a more or less strong divergence from the patient's perceived world from the shared reality, maybe one aspect which allows artists with intermittent moderate psychosis to paint stunning works of art. This divergence is largely driven by emotions or thoughts which become disassociated from the fabric of the patient's self and personality.

External vs Internal Reward

It has been shown that rewarding behavior could actually lead to decreases in that behavior in schizophrenic patients, while training and instructing the patient lead to improvements. One might speculate that training and instruction can lead to internal reward which is more motivating than external reward. Thus, even in patients suffering from psychosis, and probably especially here, motivation can be fostered and increased by using the same approaches as in people not suffering from psychosis.

Meaningful Communication

When an individual suffers from psychosis, a first important step is to help the patient see meaning in the communication process, particularly a relevance to own needs and interests. This helps to build and maintain the motivation which is necessary for a communication oriented therapeutic process. It also helps the patient build a greater sense of efficacy when interacting with his or her environment.

Since the communication process is usually significantly affected in psychosis, it may seem even more difficult to identify and interpret meaning in the messages. This is, however, not necessarily the case. To the contrary, patients suffering from psychosis often see meaning in the world in places where others do not. The drive to see meaning and meaningful connections in information from oneself and the world has not decreased, but the supply of information has.

Therapeutic alliance (TA) is an important factor in therapeutic outcome for individuals with serious mental illnesses (McCabe et al., 2012). Research has explored how certain clinical factors impact TA. Specifically, neurocognition can impact both client and therapist perceptions of TA, and that TA tends to improve over time (Davis & Lysaker, 2004, 2007). However, few studies to date have examined the relation between neurocognition and perceptions of TA in group-based cognitive skills training. The goal of this study was to examine the relation between neurocognition and perception of TA and determine how perceptions of TA may change following treatment. Hypotheses were: 1) Therapist perception of TA would be related to client baseline memory; 2) Client perception of TA would be related to their baseline memory; 3) Therapist and client perceptions of TA would be related to potential memory improvement. Client and therapist TA improved as symptoms improved following treatment, but memory ability was not related to client or therapist perceptions of TA. While these findings are somewhat contrary to past work that found memory to be related to TA, these results confirm past studies that client and therapist ratings of TA are significantly and positively related. The current study also showed that symptoms were strongly related to client and therapist perceptions of TA, and as symptoms improved, both perceptions of TA improved. This is an important finding as it indicates that a strong TA can be developed between client and therapist despite significant cognitive impairment and symptoms at the start of treatment. (Johnson et al., 2019)

Learning about Communication

The first step is to learn about communication, to see how it works, what its constituents are and the purposes it can serve. Often it helps to go through examples that may be of special relevance to the patient. Analyzing them and looking at different options and different outcomes help to illustrate to the patient the importance of the process.

For the learning process, it is important that the therapist has a sense of the patient's perceptual and emotional world. This enables the therapist to use communication styles and messages which are interpreted by the patient not as hostile, deferential or lacking in empathy. Early in the therapeutic process the interaction should help to build a strong and stable therapeutic relationship. This is already part of the learning process and should come first.

Observing Communication

Splitting up communication and being able to identify its components helps to observe the process and the variations, large and small, in it. Observing is not only a learning experience, but also helps to develop interest for it and see the possibilities in influencing and shaping interactions with others. An interaction can exist in many shapes and forms, while the underlying communication processes adhere to common rules and laws. It helps the patient to appreciate the common underlying mechanisms, which can increase trust in the process and a sense of stability in the world, and, at the same time, to see an interaction as a dynamic group of interacting communication events.

Important is that the patient learns to be able to look at the bigger picture, to observe communication as it takes place, whether it involves the patient or not. This essentially requires being able to take a step out and away from oneself to observe the dynamic without engaging in it at the same time. Over time, this becomes automatic enough that observation and engagement can alternate in one's awareness so quickly that they seem to be simultaneous.

A patient can learn about communication if the therapist reflects and comments on what happens in the communication space between the patient and the therapist. This teaches the patient patterns and skills through the expertise and experience of the therapist. However, it requires that the therapist has this expertise and experience. Especially for a psychotic patient, it is important to show this not just in theory, but also in practice through trying out new communication experiences which then translate into new perspective of the world and oneself.

Experimenting

Experimenting with communication in its different flavors can give the patient a greater sense of effectiveness with respect to the environment as well as oneself. It gives patients a greater sense of being in control, which is helpful because patients with psychosis often experience helpless and hopelessness, which can also cause some of the sudden emotional outbursts seen in severe cases of psychosis, such as schizophrenia.

A gradual increase in the scope or difficulty in the scope of experimentation probably works best. It can start with little everyday encounters and end with dating. People generally feel more vulnerable the more they feel they expose about themselves. For patients suffering from psychosis this anxiety is much greater, because they sense that their perceived world and the shared reality diverge. Own emotions may also feel real, which makes their visibility to others even more risky. The fear of getting hurt at the core of one's mental structure is universal, the hurt, however, seems more devastating in a patient suffering from psychosis because the structure is already under considerable stress.

Reflecting

The newly gained knowledge and skills around communication needs to be processed, which can help increase the confidence and sense of effectiveness in the world. This should not be solely about control, but more about seeing oneself as a part of something bigger which is not something to be afraid of, but helps individuals to address and meet their needs and wants.

The Communication Space

Depending on the environment we move through different communication spaces in everyday life. The communication space is the space in which messages are being sent and received. If one is talking to someone over the phone who lives on a different continent, the communication space extends to this person, while not including the neighbor in the apartment next door, unless the walls are really thin.

To a patient suffering from psychosis the communication space can be extremely large or extremely small, but it usually diverges considerably from that of other people. Thoughts, for example, can be influenced from a large distance, or, at the other extreme, a patient could fully disconnect from the environment. To someone suffering from psychosis the internal world largely determines the communication space, while other people's communication space is determined through an interaction with the environment.

In therapy, it is important to make the patient aware of the communication space he or she builds and what influences it. This is an important component of learning about communication and bringing about change through it.

Experiencing the World

Psychosis often leads to a vicious cycle which leads to less rather than more communication. Anxieties and a changed perception of reality can lead to a disengagement from it, which reduces the ability to distinguish internal from external reality even more. Practicing and discussing with the patient new ways to communicate, including new communication patterns and better reflection on them, increases the patient's ability to experience and bring about change in the world.

Next to improving interactions with others, a better identification and understanding of meaning helps to anchor the patient better in the shared reality, which makes everyday life and planning for the future easier.

Identifying Meaning in the World

Fears brought about by the divergence of the perceived reality from the shared reality lead to social isolation and withdrawal, which in turn reinforce feelings of fear and loneliness or frustrations. To break this cycle, it is helpful to help the patient to find more relevance in aspects of the shared reality. This is usually not a process which happens from one day to the next, but over time leads to a closer alignment of the patient's perceptions and intentions with the shared reality

Communication helps in identifying and finding meaning, either communication with oneself or with others. The exchange of messages is like a learning process in which meaning can be identified, found and accumulated. Through meaningful interactions one accumulates more meaning, more connectedness with oneself and the world and reduces the need for thoughts and behaviors which are triggered by fears, guilt, self-blame and other negative emotions. This also helps against depression and anxiety.

There are essentially two techniques to help the patient with identifying and interpreting relevance and meaning in the world. One is by directly discussing with the patient what he or she needs and wants and how this can be met in the world, the second is by helping the patient to have better interactions with the environment which make it easier to see relevance and meaning in the environment. Usually, a combination of both leads to a good outcome.

Increasing Interactions

Perceiving more meaning also makes interacting with others and oneself more meaningful. This has a positive effect on one's interaction patterns, how and in which one ways one relates to one's environment and exchanges messages with it. As the anxiety about interactions with others decreases, it should become easier to become more socially involved with others, at least to the extent which would feel comfortable to the individual also without the illness.

In the beginning this often requires reducing fears associated with situations or people that are a result of the psychotic experience. Different interpretations of information and the sources of information lead to the perception of a world which is not only less stable but seems to contain real threats, even if the latter ones are just own emotions or thoughts which have manifested as real to the patient. Meaningful interactions with the world can reduce the divergence of realities and also the fear, because they stabilize the patient's experience in the world. To be meaningful the interactions should be an exchange of messages that are relevant to the patient's interests, values or aspirations. This is one reason why it is important to discuss with the patient and get a sense for the patient's needs, wants and values. The next step is then to help the patient find and make interactions that are helpful and meaningful to him or her. With the additional focus on communication, whether in a therapeutic session, internal thoughts or between the patient and others, interactions should become easier and the fears of them lower.

Values, Needs and Aspirations

Often, individuals suffering from psychosis become uncertain about what is really important to them and the fit between these values and interests and their current life situation. In all areas of life, having one's needs, wants and values met, leads to a higher quality of life. If one values helping others in a specific way, it is important to find ways to engage in this activity, because it will result in a positive feeling. Harm to oneself and others is usually a consequence of some disconnect with one's own feelings, needs, wants and values. Burnout or verbal abuse of another person may be examples.

The change in one's relation with oneself and the environment, as well as the resulting change in the sense of self, make it usually harder for an individual suffering from psychosis to identify correctly the own needs, wants, values, and aspirations, partly out of fear that they could disturb a fragile feeling reality even more. In this situation, it is helpful to help the patient understand that connecting with them actually adds stability, rather than taking away from it. One way to reduce the fear of getting closer to and identifying key parameters about oneself is to help the patient emotionally reconnect. The emotions are the sum of vast amounts of information, such as a feeling of happiness as the product of perceptions of a situation and associated thoughts, and can, if they are owned by the patient, lead to a greater feeling of stability. Helping the patient to notice and identify them more accurately can lower fears and make the inner world, and thus also the outer world in psychosis, seem more predictable. It is important to add in this context, that emotional instability is not so much due to a too much of emotions, but a consequence of impairments in a patient's internal communication with the own emotions. The inability to read the emotions accurately leads to the sense of instability, or even the emotional and existential 'void' which is so prevalent in a patient with borderline personality disorder.

Meaningful Messages as the Instrument of Change

Communication is the vehicle of change. The instruments are meaningful messages which are generated and received by the people who take part in these interactions. In a therapeutic setting, keeping the mutual flow of information relevant and meaningful brings change in both people who take part in this process. The learning curve for the patient may be steeper in certain respects because he or she spends less time in this interaction style than a therapist.

The main objective is that patients can make communication work for themselves on their own. Looking at communication patterns and how meaning is generated in a therapeutic session should not only help with a concrete situation or problem in the moment but provide the tools to work with a multitude of situations or problems in the future. The key to build motivation and use communication processes, is to understand that meaning, information about information which is relevant to and resonates with the recipient of the message, is very much at the heart of it. Becoming better at sending and receiving, interpreting and working with meaning can make the world for an individual suffering from psychosis more stable and broadens the scope of change that can be affected on the world and oneself. Better insight and skills around communication and meaning take some time but can have a lasting beneficial effect for an individual suffering from psychosis.

Knowing Where Information Comes From

In the end, the patient should also have a better sense of communicating and knowing where information comes from. Not only does this help to reduce the divergence between the experienced world and the shared world, but it also helps to use information and communication better. Being able to identify a source of information can make it easier to identify meaning and respond to it. This helps build a stronger sense of self, better relationships and imparts greater confidence in dealing with everyday life as well towards fulfilling own aspirations. Greater insight and skills into communication can accomplish this.

Prognosis

If not treated, schizophrenia has an unfavorable long-term prognosis. When it becomes chronic, changes to the personality and some symptoms of the condition may become largely irreversible. This often also leads to loss of relationships and livelihood, and some schizophrenia sufferers begin to self-medicate with illegal drugs.

Schizophrenia has great human and economic costs. It results in a decreased life expectancy by 10–25 years. This is primarily because of its association with obesity, poor diet, sedentary lifestyles, and smoking, with an increased rate of suicide playing a lesser role. Antipsychotic medications may also increase the risk. These differences in life expectancy increased between the 1970s and 1990s.

Schizophrenia is a major cause of disability, with active psychosis ranked as the third-most-disabling condition after quadriplegia and dementia and ahead of paraplegia and blindness. Approximately three-fourths of people with schizophrenia have ongoing disability with relapses and 16.7 million

people globally are deemed to have moderate or severe disability from the condition. Some people do recover completely and others function well in society. Most people with schizophrenia live independently with community support. About 85% are unemployed. Some evidence suggests that paranoid schizophrenia may have a better prospect than other types of schizophrenia for independent living and occupational functioning. In people with a first episode of psychosis a good long-term outcome occurs in 42%, an intermediate outcome in 35% and a poor outcome in 27%. Outcomes for schizophrenia appear better in the developing than the developed world. These conclusions have been questioned.

There is a higher than average suicide rate associated with schizophrenia. This has been cited at 10%, but a more recent analysis revises the estimate to 4.9%, most often occurring in the period following onset or first hospital admission. Several times more (20 to 40%) attempt suicide at least once. There are a variety of risk factors, including male gender, depression, and a high intelligence quotient.

Schizophrenia and smoking have shown a strong association in studies worldwide. Use of cigarettes is especially high in those diagnosed with schizophrenia, with estimates ranging from 80 to 90% being regular smokers, as compared to 20% of the general population. Those who smoke tend to smoke heavily, and additionally smoke cigarettes with high nicotine content. Some propose that this is in an effort to improve symptoms. Among people with schizophrenia use of cannabis is also common.

Into the Future

From the discussion it should be obvious that there is still much to be done in improving the treatment of psychosis and schizophrenia. However, particularly on the side of psychotherapy, there is a widespread lack in using the tools we already have available. This is non-excusable, and the argument of a lack of resources does not make it better.

A greater focus on communication, internal and external, can help to move the treatment of schizophrenia forward in ways that may not even be fathomed yet.



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