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Commentary **Open Access**

Rethinking the Concept of Psychosis and the Link Between Autism and Schizophrenia

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While searching for a connection among the four articles included in the present issue of SJCAPP—and under the inspiration of both Craddock and Owen (1) as well as selected previous research on psychosis—I found myself on a trail leading back to Kraepelin.

Prior experiences and delusion content

The Italian pilot study by Catone and colleagues (2) in this issue focuses on the relationship between stressful experiences and delusion content in adolescents with psychotic disorders. The authors hypothesize that a biographic continuity or "thematic link" can develop between the themes of previous life experiences and the content of a patient's delusions. They examine the relationship between the prior experiences and delusions of a sample of 16 patients experiencing their first psychotic episodes. The researchers expected to find a statistically significant association between past experiences and psychotic symptom content, and they did discover a significant association between humiliating experiences and persecutory delusions. The authors suggest that the thematic link concept may provide clinicians with a greater awareness of the patient's thoughts and emotions and that addressing past experiences and linking them to emerging or consolidated delusions may make experiences like bullying less frightening for the patient.

How to make sense of delusions

Although bullying may sometimes lead to psychosis, it more than likely will not. What triggers the development of psychosis? How and why are past experiences linked to psychosis in some patients? How do these experiences influence the content of a patient's delusions?

With regard to the psychopathology of delusions, the authors of the Italian pilot study (2) introduce Jaspers' notion of "understandability" (3). They discuss the essential problem of whether it is possible to distinguish between primary or true delusions and secondary or delusion-like ideas (2). They ask whether the application of the term *understandability* should be related to the patient's psychological history or to his or her life history, and they suggest the thematic link for use as a new way of interpreting classical psychopathology. The patient's history may offer a historical understanding that is easier to comprehend as compared with a psychological understanding in phenomenological terms.

In a recent article, Mishura and Fusar-Poli (4) also discussed Jaspers' notion of understandability. They related his phenomenological approach to current neurobiological research. Those authors refer to Kapur and colleagues' concept of "aberrant salience" (5). They suggest that primary delusions develop during the prodromal state to provide an explanation of the experience of the aberrant salience of innocuous stimuli that results from abnormal dopamine firing in the striatum (4).

When considering the notion of understandability, in addition to the insight given by the patient's psychological and life histories and the possible experience of aberrant salience, does it make sense to include knowledge about how an experience at both the conscious and unconscious levels forms through neurocognitive processing? If so, it will be important to realize how delusion content may be affected by cognitive impairment during the cognitive process of

integrating the previous and present conscious and unconscious experiences.

The origin of delusions

The authors of the Italian pilot study (2) refer to two main hypotheses regarding the origin of delusions: the basic reasoning hypothesis and the anomalous experience hypothesis. Both of these hypotheses were formulated by Maher in an article that focused on the relationship between delusions and hallucinations (6). The basic reasoning hypothesis suggests that a basic defect exists in the reasoning of deluded individuals. According to Maher (6), this hypothesis dates back to Kraepelin (1889). The second hypothesis—the anomalous experience hypothesis—states that the delusion arises in response to an attempt to explain anomalous conscious experiences (6). In addition to these two hypotheses, the authors of the Italian study refer to a third transdiagnostic approach to delusions that was presented by Garety and Freeman (2). In a recent review of the empirical cognitive psychology literature about delusions, Garety and Freeman (7) updated the empirical evidence regarding the relevance of a cognitive model of positive psychotic symptoms that they had previously developed together with their co-researchers (8). This model highlights the contribution of psychological mechanisms that involve both emotional and cognitive reasoning processes (8). When applying this model to persecutory delusions, Freeman and colleagues (9) suggested that explanations considered during the search for meaning may be influenced by specific cognitive biases associated with psychosis, including theory of mind dysfunction as well as the jumping-to-conclusions bias and the attributional bias. At least three mediators may be involved in the choice of explanation: individual beliefs about mental illness, social factors, and little belief flexibility. The assumption that the emergence of symptoms depends on an interaction between vulnerability and stress underlies this model. However, as stated by the authors, it remains to be determined whether the cognitive biases associated with persecutory delusions are state or trait variables, and it is also not yet understood how psychotic processes, non-psychotic processes, and the environment affect each other. To predict how and when precipitants in interaction with a given vulnerability lead to psychosis, the dynamics of these interactions will have to be included in the model.

Subtyping thought disorders as a means of identifying subgroups

The Danish study by Bundgaard Andersen and colleagues (10) in this issue explores the contributions of the Thought Disorder Index of the Rorschach Inkblot Method to clinical assessment, and it examines whether the Rorschach test is helpful for the assessment of early-onset schizophrenia as a result of its ability to detect thought disorder. In addition, the researchers examine whether the Thought Disorder Index is superior to the Comprehensive System, which is another simpler index of the Rorschach test. Although a small sample size limits the conclusions that can be drawn, the authors report results that indicate that specific types of thought disorder may be specific to schizophrenia, and they state that the Thought Disorder Index may be superior to the Comprehensive System. The authors conclude that, if their findings are replicated in larger studies, there may be implications for other assessments and for the subtyping of schizophrenia. Such findings may help to define the underlying mechanisms of the disorder itself.

However, questions may remain about whether the identified subtle differences in the types of thought disorder are of any specific clinical or research relevance. This will be the case only insofar as these different types by themselves represent relevant targets for treatment or research. For example, do they represent specific domains of symptoms of relevance for the identification of early signs of psychosis or for preventive interventions in at-risk individuals? Do they reflect specific biomarkers that can be used in research efforts to identify subgroups?

Exploring "experienced reality"

Forty years ago, while analyzing the concepts of disturbed states of consciousness and psychosis, Aggernæs (11) suggested future clinical research should be inspired by the academic psychological literature addressing concepts related to defects in integration or differentiation and lack of coherence. Since then autism research has benefited from this type of approach. An example of this is reflected by the central coherence theory suggested by Frith in 1989 (12). Cognitive theories of autism have guided autism research (13). One of the three main cognitive theories of autism focuses on impairments related to integrative processing (e.g. Frith (12)), another on executive dysfunctions.

With inspiration from Piaget, Aggernæs and colleagues (14) developed a reliable clinical technique to investigate experienced reality and unreality qualities that are connected to everyday life experiences in psychotic and non-psychotic individuals. In contrast with projective techniques like the Rorschach test, the developed instrument provided a direct evaluation of reality testing and a more general evaluation than that obtained by methods that had been constructed to uncover hallucinations and delusions. The researchers went on to explore experienced reality in a series of clinical

studies, including studies of 3- to 6-year-old children, non-psychotic adults, and patients with schizophrenia (14-16). The researchers found marked differences in the reality testing of children, non-psychotic adults, and schizophrenic patients. By the age of 3 years, children have already experienced real items as being real with regard to the reality qualities of behavioral relevance, publicness, objectivity, and existence in the same way that has been observed in non-psychotic adults. In addition, normal 3-year-old children showed a pronounced tendency to feel able to change the real world simply through acts of thought (magical thinking); this tendency was observed to have declined rapidly and nearly disappeared in 6-year-old children. The 3-year-old children showed a pronounced tendency to experience imaginary items as being like real items and to think that they were not able to change such items simply by wanting them to change. This rigidity of thinking seemed to reach a peak in 5-year-old children and to decline thereafter; it was a rare finding in non-psychotic adults.

In patients with schizophrenia, Aggernæs and colleagues (16) observed that patients with schizophrenia were more prone to experience non-existing items as being real than to experience existing items as being unreal. In other words, these patients were more prone to a rigidity of thinking than to magical thinking. In conclusion, the authors stated "that "the real world" continues nearly completely to be real for schizophrenic patients but that there is an important tendency to experience the imaginary, non-existing world as being real too" (16).

The link between autism and schizophrenia

Is it possible that this rigidity of thinking may reflect the core of a link between autism and schizophrenia? Could this be what connects the two disorders at the phenomenological level? In patients with autism, this rigidity is observable at the clinical level as a concrete, inflexible, and at times even literal type of thinking that—regardless of the patient's cognitive level—may reflect difficulties with the handling of symbolic or abstract language concepts. Although it is sometimes directly observed in patients with schizophrenia, the rigidity of thought identified by Aggernæs and colleagues may be less apparent at the clinical level. However, from a neurocognitive perspective, these cognitive impairments may be comparable in nature but less severe to those seen in patients with autism. In other words, cognitive impairments of the same type and origin may operate at different levels of cognitive complexity in patients with autism and patients with schizophrenia. This would be comparable to the different levels of complexity of thought and reasoning distinguished by Piaget and suggested by him to relate to several different cognitive stages of development (17). Torres and colleagues (18) referred to Piaget's theory of intelligence and the development of thought in a study that compared a group of schizophrenic patients with a group of healthy controls using the Longeot Logical Thought Evaluation Scale, which is a non-verbal psychometric instrument. Their results showed marked differences between the two groups, with the schizophrenic patients performing at lower cognitive levels as compared with the control group. These findings were consistent with those of Aggernæs and colleagues (16).

The suggested view of a link between autism and schizophrenia may be consistent with a model of the complex relationship between biological variation and some major forms of psychopathology that was recently proposed by Craddock and Owen (1). Those authors also support the need to reconsider a relationship between psychotic disorders and other neuropsychiatric phenotypes (e.g., autism). They refer to evidence that shows that structural genomic variants are a common cause of genetic variation in humans and that such variants are present in neuropsychiatric phenotypes, including autism, intellectual disability, and schizophrenia.

Beliefs and practices of treatment

It has long been recognized that cognitive deficits may be involved in the development of psychosis and the pathogenesis of schizophrenia (19). Even so, treatment seldom directly addresses the specific cognitive deficits involved and instead focuses on the level of psychosis, with the aim of reducing the abnormal experiences with the use of antipsychotic medical treatment. Alternatively, treatment may indirectly address cognitive impairments with the use of social support or psychotherapeutic strategies to help patients cope with their symptoms.

In the third article in this issue, Haapasalo-Pesu and colleagues (20) demonstrate a several-fold increase in the prescription of antipsychotics for children and adolescents that occurred during the 10-year period from 2000 to 2010, according to their nationwide register study from Finland. The authors state that the prescription of antipsychotic medication to minors is common and that there is frequent off-label use of antipsychotics, despite accumulating evidence of serious side effects. The lack of scientific data supporting these prescriptions is a serious problem that is addressed by the authors.

The growth in the prescription of antipsychotics may reflect a strong belief in hypotheses that suggest that mental illnesses, including psychoses, result from the dysfunction of certain neurotransmitter systems. However, antipsychotic medications have been shown to be of only moderate effect for the treatment of schizophrenia. Unfortunately, as stated

by Garety and Freeman (7), no major breakthrough took place for the treatment of schizophrenia from 2000 to 2010, regardless of whether medication, psychological therapies, or social interventions were considered.

Developmental disorders in "adult disguise"

Symptoms of schizophrenia may evolve via several different pathways, thereby reflecting the fact that brain events initiated at different levels are involved in the pathogenesis of the disease.

Increasing evidence suggests that information-processing deficits, neurocognitive impairments, and genes involved in schizophrenia may be of essentially the same nature as those observed in children with neurodevelopmental disorders. Therefore, it may be plausible to assume that differences in the severity of illness, the comorbidity of conditions, age-related symptom expression, and a focus on psychosis may be what separate childhood neurodevelopmental disorders from schizophrenia at the clinical and phenomenological levels. If so, schizophrenia may in fact be childhood neurodevelopmental disorders in "adult disguise." This is consistent with the observed heterogeneous character of schizophrenia, the suggestion that the term may apply to several varied conditions (21-23), and the varied effects of antipsychotic medical treatment that have been observed in affected patients (24-25). Differences in the severity and type of information-processing deficits and neurocognitive impairments, together with the overall degree of neurobiological involvement, may contribute to the polymorphous and heterogeneous character of schizophrenia. Consistent with this hypothesis is that fact that increasing evidence suggests that schizophrenia shares common genes with autism and attention-deficit/hyperactivity disorder (26-34). Furthermore, autism, attention-deficit/hyperactivity disorder, and schizophrenia may share neurocognitive impairments (35-43) and certain symptoms (44-46).

From a genetic perspective, many genes—and not always the same ones—may be involved, with each one contributing only small psychopathological effects (23). Recent results from genome-wide association studies support this hypothesis and show genetic overlap among several major psychiatric disorders, including schizophrenia and autism spectrum disorders (30,33). Increasing evidence suggests that rare genetic variants of moderate to large effect size may play an important role in the development of neuropsychiatric disorders as demonstrated by several studies involving the genome-wide analysis of copy number variants (28,31,34). These results show an overlap in copy number variant loci in patients with schizophrenia, attention-deficit/hyperactivity disorder, and autism (28,31,34). The gene expression may depend on complicated interactions between genetic and environmental factors; for example, it is likely that schizophrenia develops as a result of an interaction between genetic liability and the negative impact of environmental factors (47).

From a neurobiological perspective, deficits in information processing make up a basic vulnerability that is present before the development of manifest disease (19). Consistent with the present hypothesis is the idea that information-processing deficits are not specific to schizophrenia; they may also be present with other neuropsychiatric disorders (48-50). Several neurocognitive and psychophysiological measures are considered candidate endophenotypes in patients with schizophrenia (36-37,51).

The significance of basic cognitive impairments (e.g., dysfunctions of executive functions, working memory, or perception) may depend on and be related to the level of global intellectual functioning. This is consistent with evidence that indicates that a lower premorbid level of intelligence may increase vulnerability to schizophrenia (52). In addition, intelligence may genetically overlap with known cognitive endophenotypes for schizophrenia (53).

Alcohol and drug abuse may further contribute to the development of manifest disease, with alcohol acting via a genetic pathway at the neurobiological level and via the environment at the social level (54).

Psychosis as a social signal

From a neurodevelopmental point of view, over the course of an individual's development, cognitive challenges increase from childhood through adolescence and into adulthood. The relationship between the development of the brain and resulting behavior is complex, with evidence suggesting that changes in the structural brain mirror functional changes that coincide with improvements in cognitive and behavioral skills (55). Although subcortical structures appear similar to their adult forms at birth, the cerebral cortex is immature in terms of connectivity between and within regions, and it continues to develop into adulthood. According to Parson and colleagues (55), the timing and changes of connectivity during the course of development and their relationship to environmental factors (e.g., the important parent-child relationship) require much further exploration, including the obtaining of longitudinal structural information and more fine-grained temporal and spatial information about the functional neuroanatomy of infant brain activity.

As suggested by Garety and Freeman (7) and Freeman and colleagues (9), stress, anxiety, and depression may worsen already present cognitive impairments, thereby contributing to the appearance

of symptoms and increasing the risk for manifest disease. Stress may be triggered by major life events, trauma, or drug misuse.

With reference to the different cognitive stages of development suggested by Piaget (17), it may be hypothesized that—across the course of development and with normal distribution at different levels of cognitive complexity—some individuals may reach the limits of their cognitive abilities. In addition to stress that results from major life events and trauma, some individuals may be predicted to experience more enduring stress merely as a result of events related to normal development. A cognitive challenge may arise for adolescents and young adults when they leave home and have to cope all by themselves in an increasingly complex reality. Until then, family and school may have compensated for minor impairments in cognitive function or social ability. With increasing age, social expectations are likely to increase; this time increases pressure on the executive functions involved in the tasks of planning and flexible adjustment according to context in addition to the need to be able to handle abstract thoughts and to engage in hypothetical reasoning and metacognition. Under these conditions, stress may develop as a result of a discrepancy between the cognitive abilities of and the cognitive challenges presented to vulnerable individuals.

Why do apparently normal and even very intelligent people develop psychosis? Why do they not question their unrealistic ideas? Why is it that people in the social environment—including health care professionals—often do not realize until full symptoms appear that individuals who go on to develop schizophrenia are vulnerable and at risk?

As proposed by Kapur and colleagues (5), psychosis may be a dopamine-mediated state of "aberrant salience" of stimuli and ideas. Antipsychotic medications may dampen the salience of these symptoms via the modulation of the mesolimbic dopamine system. The experience of aberrant salience that results from an increased dopaminergic level may contribute to the realistic quality of an experience, thereby reinforcing the sense of reality of the experience. This may contribute to a resistance to questioning the content of the experience. In this way, psychosis may act as a signal that is transmitted at the social level that makes the rest of society aware of processes taking place within an individual.

Rethinking the concept of psychosis

Psychosis may develop as a result of a primary dysfunction in the dopaminergic system and related transmitter systems, with reactions to these dysfunctions molding the individual's experience (5). This prevalent hypothesis is consistent with the previously mentioned anomalous experience hypothesis (6), and it may be in line with the suggestion by Mishura and Fusar-Poli of a relationship between the experience of aberrant salience and primary delusions (4).

In addition to hypotheses suggesting that psychosis results from dysfunctions in neurotransmitter systems, is it possible for psychosis to consist of a purely natural phenomenon that involves sensing or understanding the salient features of a cognitive experience that may reflect a distorted picture of reality? If this is the case, cognitive impairments with no measurable abnormal changes within the neurotransmitter systems may be sufficient for psychosis to develop. The individual may not be aware that his or her thinking deviates from normal. In contrast with—although inspired by—the hypothesis suggested by Kapur and colleagues (5) is the idea that psychosis may consist of a state of "normal salience" of aberrant experienced stimuli or ideas. The experience of normal salience may involve a transient elevation in the dopaminergic level within the normal range that may contribute to the realistic quality of the experience by enhancing its salience. Because changes in the dopaminergic level may not necessarily be present for this kind of psychosis to develop, antipsychotics may be less effective. This last definition of psychosis may be in line with the basic reasoning hypothesis suggested by Maher (6) while referring to Kraepelin (1889). It may also be consistent with the suggestion that the rigidity of thought observed in patients with schizophrenia may reflect the same cognitive impairments that are seen at a more severe level in patients with autism and with the observation that patients are more prone to experiencing non-existing items as being real than to experiencing existing items as being unreal (16).

ESSENCE and developmental history

Society may affect mental illness by defining mental disorders, including psychosis and schizophrenia, as diagnostic constructs or phenomena (i.e., as categorical or dimensional representations of psychopathology or gestalts) (1,22,56-59). It is likely that symptoms may develop in processes depending on how they are conceived and defined and that these processes may therefore themselves influence the course of illness.

A few years ago, Gillberg (57) introduced the term *ESSENCE*—Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations—to cover a group of often-overlapping neurodevelopmental syndromes observed in preschool children and to point out the risk of overlooking some symptoms while focusing on others. With the introduction of the acronym, Gillberg sought to acknowledge that these

syndromes are to some extent arbitrary endpoints or cutoff points on normal distribution curves, with most syndromes comprising a mixture of symptom collections from different normal distribution curves. Rather than being discrete categorical disorders, these syndromes represent brain dysfunctions and neurodevelopmental problems. Children who present with ESSENCE problems require assessment from a multifactorial and multidisciplinary point of view.

Instruments that can be used to collect developmental history information, like the Motor Skills History Form and the Developmental and Motor History Form offered by Reiersen, author of the final article in the present issue (60), may be useful to enhance the level of developmental and psychiatric history gathered during clinical assessment. The author is in line with Gillberg when she states that such tools may assist with decision making related to further diagnostic testing in addition to providing information that is relevant to treatment needs and patient prognosis. Although the collection of developmental history information is an important part of the clinical assessment of neurodevelopmental disorders in children, it may not necessarily be part of the clinical evaluation of an adult patient with schizophrenia. The traditions of clinical assessment in the fields of child and adolescent psychiatry and adult psychiatry may differ, with a stronger emphasis being placed on developmental history assessment for pediatric patients.

Future perspectives

The field of psychiatry appears to be at a crossroads. To secure the progress of psychiatric research and clinical practice, there is a need to revise concepts, methods, and overall models and to integrate knowledge from different fields. A fruitful approach may involve focusing research on the interface between normal and deviant thinking and relating processes at the genetic, physiological, cognitive, psychological, and social levels. As suggested by Craddock and Owen (1), models of mental illness will have to consider both normal and abnormal brain function, and psychiatry research will have to integrate evidence from various levels (e.g., molecular biology, cognitive and affective neuroscience) to move toward a coherent understanding. Such a strategy could focus on what separates normal from deviant thought processes and whether both can be present at the same time. Future research is encouraged to focus on the tasks of identifying when, how, and why thought and perceptual processes deviate from typical development; defining normal and abnormal; and suggesting methods to identify the mechanisms behind all possible levels involved. The suggested neurodevelopmental approach, the cognitive link between autism and schizophrenia, and the added general concept of psychosis may serve as steps in this direction.

From a clinical perspective, the application of complex multilevel models in research may add to our knowledge of the multifaceted nature of mental illness. It may also encourage clinicians to employ multiple strategies for the treatment of schizophrenia and related disorders and to differentiate treatment according to more specific knowledge of the different subtypes of disease and their etiologies.

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