Because almost one-third of individuals affected by 22q11.2 deletion syndrome (22q11DS) develop schizophreniform disorders, the field of psychiatry and cognitive psychopathology has become increasingly interested in uncovering the mechanisms leading to psychosis in this population. Many view this deletion syndrome as a model for understanding the development of schizophrenia. The relevance of 22q11DS to the field of schizophrenia research was first established by demonstrating that the psychotic-like manifestation in this deletion syndrome represented frank psychotic manifestations as opposed to residual symptoms originating from mental retardation. These initial efforts were followed by a larger study involving 50 adults affected with 22q11DS. The complete psychiatric evaluations performed with this sample revealed that 15 participants (30%) met the diagnostic criteria for a psychotic disorder, with 12 (24%) meeting the schizophrenia criteria. Employing a different investigational strategy, Karayiorgou et al. randomly assessed for 22q11DS in 100 individuals with schizophrenia, and found that two individuals never before screened for the deletion actually tested positive for 22q11DS. In another study, medical records were initially screened for patients with the cardinal features of 22q11DS (cardiac anomalies and cleft palate), and then cross-referenced with records from the psychiatric hospitals. When screening for 22q11DS in these potential cases, the authors found that 14% of the patient sample with schizophrenia was also affected with 22q11DS. Finally, in a large group of children with childhood-onset schizophrenia (COS), four participants out of 75 (5.3%) were found to also have 22q11DS. The observations collected to date establish solid evidence to the effect that schizophrenia affects individuals with 22q11DS. They further suggest that, with the exception of having a monozygotic twin with schizophrenia or two parents with schizophrenia, 22q11DS represents the strongest genetic risk factor associated with psychotic disorders.

As is often the case in psychiatry, we confer ‘psychiatric risk’ status to children and adolescents exhibiting the cardinal features of adult psychiatric disorders. Today, fields of investigation such as those concerning paediatric bipolar disorder or high-risk adolescents in the schizophrenia prodrome are gaining significant momentum based on the assessment of subclinical symptom expressions using adult diagnostic criteria. Interestingly, the field of 22q11DS research has developed in a similar fashion. By identifying the clinical importance of schizophrenia in this deletion syndrome, we naturally assume that children and adolescents with the deletion run a very high risk of developing schizophrenia. In many respects, the application of an adult symptom framework to childhood and adolescent symptom expression has proved useful, especially in demonstrating that pathological neurodevelopmental processes linked to schizophrenia can begin years before the onset of the full-blown disorder. This also helped to establish a continuum view of psychotic symptoms as opposed to a dichotomist approach.

The strict application of adult criteria to childhood psychopathology, however, has some limitations. In addition to potentially pre-determining childhood psychopathology on the basis of adult criteria, a strict application carries the risk of obstructing our capacity to assess the processes at work during the unfolding of initial symptoms. Taking hallucinations as an example, restricting our assessment to diagnostic or non-diagnostic hallucinations may impede our ability to discern the cognitive and emotional factors contributing to the unfolding and maintenance of such symptoms. In turn, ignoring these initial contributing factors may have undesirable consequences on our therapeutic action. Indeed, cognitive and emotional factors contributing to the development of psychotic symptoms may represent interesting therapeutic targets in the context of preventative interventions during the early stages of psychosis. Recent cognitive models of psychotic symptoms provide a complementary perspective on the issue by offering a conceptual framework that attempts to understand the unfolding of positive symptoms of psychosis. These models are in line with a continuum view of psychotic expression, founded on epidemiological research that shows the prevalence of hallucinations and delusions in the general population, in both children and adults.

Cognitive models of psychotic symptom formation and studies of high risk of psychosis suggest that positive schizotypy (subclinical expression of delusions and/or hallucinations) in youngsters constitutes a potent predictor for subsequent onset of psychosis. In adolescents with mild...
intellectual impairment, the presence of schizotypal cognitions significantly predicts the onset of frank psychotic symptoms. In adolescents raised in families with increased prevalence of psychotic disorders, schizotypy index scores also significantly predict the later onset of a psychotic disorder. Finally, prospective longitudinal data show that 42% of adults meeting a diagnosis for schizotypal disorders at 26 years of age had reported at least one symptom of hallucination or delusion at 11 years of age. Similarly, the most recent longitudinal data on adolescents with 22q11DS validate the predictive power of positive schizotypy symptoms as a marker for increased psychosis-proneness. In a group of 31 children with the deletion syndrome, baseline subthreshold psychotic symptoms significantly predict the presence of a psychotic disorder at follow-up. Such observations may provide part of the answer as to why children and adolescents with 22q11DS run an increased risk of schizophrenia. However, these observations cannot account for the processes at work in the unfolding of positive symptoms.

In an effort to provide a complementary perspective to risk of psychosis in children and adolescents with 22q11DS, we propose reviewing the available literature that suggests increased psychosis-proneness in children and adolescents with 22q11DS; that is, to identify the factors contributing to the appearance of symptoms of hallucinations and delusions in youths with the deletion. We will make reference to Frith’s model of auditory hallucinations to assess psychosis-proneness in youths with 22q11DS. Furthermore, we will detail a stress-vulnerability model (inspired from Freeman et al.) in an attempt to gather the various pieces of evidence that signify increased psychosis-proneness in youths with 22q11DS.

**Psychosis-proneness in Youths with 22q11DS – Increased Vulnerability to Auditory Verbal Hallucinations**

To the best of our knowledge, three studies outline the basic evidence concerning psychosis-proneness in youths with 22q11DS. Baker and Skuse provided the first description of positive schizotypy in a group of 25 individuals with 22q11DS aged between 13 and 25 years, along with a control group matched for age, gender and estimated intelligence quotient (IQ). Employing a schizotypy rating obtained from the Child and Adolescent Psychiatric Assessment (CAPA), validated with the junior schizotypy schedule self-report questionnaire, the investigators found that 12 of 25 participants (48%) from the 22q11DS group reported subclinical expressions of positive schizotypy. These include delusions (persecution, superstition), auditory and visual hallucinations and perceptual aberrations such as depersonalisation and thought broadcasting.

In another study, examiners employed the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version to assess psychotic symptoms in 60 participants with 22q11DS aged between nine and 18 years. They observed that 26.7% of the sample reported positive schizotypic manifestations composed of mostly verbal auditory hallucinations, together with some reports of visual hallucinations and persecutory delusions. The rate of positive symptoms of psychosis in youths reported in this study compares favourably with that reported by Debbané et al. in their assessment of psychotic symptoms in a younger group of children and adolescents with 22q11DS (mean age 10.62 years; range six to 19 years). These authors found that almost 28% reported at least one positive schizotypic manifestation. Specifically, four individuals reported both hallucinations and delusions, five reported hallucinations only and three reported delusions only. All nine individuals with hallucinations reported symptoms generally qualified as disturbing and unpleasant; one individual also reported visual hallucinations. Of the seven individuals reporting delusions, four reported delusions of reference, three reported grandiose delusions, two reported persecutory delusions and two reported somatic delusions. Importantly, these positive symptoms appeared in the context of other psychopathology, including anxiety disorders, attention-deficit–hyperactivity disorder (ADHD) and mood disorders.

To summarise, the three studies mentioned above reported elevated psychosis-proneness in children and adolescents, which can be observed as early as nine years of age. These studies presented critical information that ultimately led to descriptive rather than explicative accounts of psychotic symptoms unfolding in 22q11DS.

Most contemporary cognitive models attempting to account for the mechanisms promoting positive symptoms rely on the conceptual framework introduced by Frith. Briefly, Frith argues that dysfunctions in identifying internal mental events as self-generated may engender a sense of lack of control in the experience of self-generated speech, thoughts and intentions. In turn, such dysfunctions (self-monitoring deficits) may set the stage for positive symptom formation such as delusions of control or verbal auditory hallucinations. Recent cognitive studies demonstrate the prevalence of self-monitoring deficits in patients with schizophrenia. In psychiatric disorders, self-monitoring dysfunctions appear to be relatively specific to positive symptoms of psychosis, and can also be observed in non-clinical populations who report increased hallucination-proneness. To date, only one study has reported on the evaluation of self-monitoring in 22q11DS. As in other psychosis-prone populations, adolescents with 22q11DS (aged between 12 and 18 years) exhibit self-monitoring deficits in comparison with controls matched for IQ and age. The results suggest that when asked to imagine the performance of actions, adolescents with the deletion confuse external contexts. Interestingly, positive schizotypy intensity is also correlated with such self-monitoring confusions when hallucination-prone adolescents are set the same task. This implies a common self-monitoring deficit between 22q11DS adolescents and hallucination-prone adolescents from the community.

In this perspective, a neurocognitive account of auditory hallucinations may yield a better understanding of psychosis-proneness in 22q11DS. As suggested above, auditory hallucinations represent the earliest symptomatic manifestation of psychosis in children with 22q11DS, and represent a powerful predictor for subsequent development of psychosis. Aleman and Larø contend that hallucinations in psychosis are likely to originate from a combination of elements, including emotional factors, self-monitoring deficits and top-down factors such as pre-existing beliefs or attention processes. More specifically, the interactions between
these different factors may lead an individual to confusions between internal representations (internal mental events or images) and bottom-up percepts (perception originating from the exterior), thus providing the hallucinatory experience. For example, research with schizophrenic patients and hallucination-prone college students illustrates how negative emotional content exacerbates self-monitoring deficits; specifically, hallucination-prone individuals are more likely to attribute self-generated negative contents to external agents. Some authors argue that such external misattributions, when applied to ego-dystonic negative content or intrusive thoughts, may underlie some forms of verbal auditory hallucinations. The neuroanatomical underpinnings of such misattributions, including the amygdala at the emotional level and the anterior cingulate cortex and superior temporal gyrus at the monitoring level, also correspond to vulnerability sites in the cerebral structure associated with 22q11DS. To date, two studies have found altered amygdala volume in children with 22q11DS, and one longitudinal follow-up observed a greater decrease in amygdala volumes in youths with the deletion. Two other studies found grey matter reduction in the cingulate gyrus, specifically in the anterior portion. Other investigations have reported abnormal maturation patterns in the superior temporal gyrus in younger children with 22q11DS, and recent preliminary data suggest that a decrease in superior temporal cortical thickness is specifically associated with auditory hallucinations in this syndrome. Neuroimaging studies performed to date have demonstrated cerebral alterations that potentially disturb self-monitoring mechanisms in youths with 22q11DS, and clinical studies have highlighted hallucination-proneness in these youngsters. Future studies may further describe the interaction between cerebral alteration, self-monitoring dysfunctions, emotional disorders and the unfolding of hallucinations in children and adolescents with 22q11DS.

The Unfolding of Positive Symptoms of Psychosis in Youths with 22q11DS – A Multifactorial Account

With respect to the wealth of schizophrenic-like cognitive deficits and neuroanatomical alterations; as well as identified genetic factors putting individuals with 22q11DS at increased risk of psychosis, it seems clear that only a multifactorial framework can account for psychosis-proneness in this syndrome. Here, a stress-vulnerability model inspired by a cognitive account of persecutory delusion formation allows us to start putting together the pieces of the puzzle collected to date in 22q11DS.

Such a model may assist us beyond the iterative collection of evidence linking 22q11DS to schizophrenia at the descriptive level. It can also provide further meaning of what it is to be prone to psychosis as a youngster with 22q11DS. Figure 1 shows an adapted diagram of the stress-vulnerability model, while Figure 2 attempts to tailor the framework to include the evidence collected to date concerning psychosis-proneness in 22q11DS.

In their cognitive account of persecutory delusion formation, Freeman and colleagues conceptualise the precipitant (starting point) of psychotic symptom unfolding as a stress-vulnerability interaction between genetic, biological, psychological and environmental factors that can directly lead to an aberrant perceptual experience and/or to states of heightened arousal (see Figure 1). The first central nod of this model is to suggest, following Maher (1974), that delusional beliefs represent the individual’s attempt to elaborate an explanation concerning aberrant perceptions and/or abnormally high arousal states. It is also recognised that precipitants may not always lead to aberrant experiences (extreme environmental stressors, for example), and still constrain individuals to explain the precipitant event. Precipitants may also indirectly influence their throughput through their relationships with emotions (states and personality) and metacognitions (beliefs about the self and others), as well as with cognitive deficits related to psychosis (executive dysfunctions, attention deficits, self-monitoring dysfunctions). We have already reviewed how some cognitive deficits may participate in the unfolding of perceptual aberrations such as hallucinations. Freeman and colleagues show how emotional factors, particularly anxiety and depression, contribute to the process of positive symptom formation. Experts in schizophrenia prodrome research observe that clinically relevant anxiety symptoms often precede the onset of positive symptoms. Specifically, anxiety is thought to exert a decisive influence in the selection of an explanation leading to delusional beliefs. As shown in research on anxiety disorders, the cognitive component of anxiety orientates the individual to entertain thoughts about danger and to anticipate threats. In other words, worry themes express the anticipation of danger, which constitutes the principal component reflected in persecutory delusions. Anxiety may also influence beliefs about the self and others (metacognitive beliefs). In certain cases, worry itself may become the object of belief: ‘I am going crazy’. This type of anxiety, referred to as ‘metaworry’, is found to be more prevalent in those at high risk of schizophrenia and in schizophrenic individuals. Anxiety may also influence other delusional beliefs; if we consider the case of ideas of reference, increased anxiety and threat anticipation may transform reference beliefs such as ‘people pay particular attention to me’ into more hostile elaborations such as ‘people looking at me are out to get me’ in this multifactorial model, Freeman and colleagues thus articulate the precipitant–emotion–cognitive dysfunction triad that contributes to the formation of positive schizotypic manifestations.

In 22q11DS research, much attention has been paid to the genetic and cerebral precipitant factors yielding increased risk of psychosis in this syndrome. Recent longitudinal research has reported interactions
Schizophrenia

Figure 2: Stress-vulnerability Model of Positive Symptom Formation Adapted to Identified Psychosis-proneness Factors in 22q11DS

At the top are the precipitant factors of environmental, cerebral and genetic origin. To the right are the cognitive dysfunctions identified in youngsters with 22q11DS as contributing to the emergence of psychotic symptoms. To the left are the emotional factors implicated in the formation and maintenance of positive schizotypic manifestations in the deletion syndrome.

between these precipitant factors. Youngsters with the deletion carrying the low-activity catecho-o-methyltransferase gene (COMTL), who may be exposed to increased levels of dopamine in the prefrontal cortex, appear to be more liable to psychotic disorders. The authors further observe an association between COMT and reduced cerebral grey matter volume in the dorsolateral prefrontal cortex, leading to the further observe an association between COMTL and reduced cerebral cortex, appear to be more liable to psychotic disorders. More recently, Gothelf et al. observed that COMT genotype, verbal IQ (VIQ) decrease and anxiety/depression score as measured by the Child Behaviour Checklist – Parent Version (CBCL) combine to predict 54% of the variance of the Brief Psychiatric Rating Scale (BPRS) total score. Interestingly, the COMT genotype, VIQ decrease and CBCL anxiety/depression score respectively correspond to precipitant dysfunction, cognitive dysfunction and emotional factors in the stress-vulnerability model. Gothelf and colleagues also explored significant interactions between these factors and baseline psychotic symptoms. With regard to emotional factors, the authors found that the “baseline anxiety/depression scores x the baseline psychotic symptoms scores” interaction significantly predicted BPRS scores at follow-up. While the authors interpreted these results as conveying a specific genetic predisposition to a psychiatric phenotype, the question of why baseline emotional factors should interact with baseline psychotic manifestations remains untouched.

Complementary interpretations may focus on the nature of the interactions between emotional factors and positive symptoms of psychosis. According to Freeman and colleagues, the content of positive symptoms reflects the emotional perturbations of the individual. For example, important feelings of anxiety can provide threat-related content to persecutory delusions, while feelings of being punished for intrinsic badness can originate from poor self-esteem. The presence of emotional disorders, as evidenced in children and adolescents with 22q11DS, intimates the activity of depressive and anxiety-laden metacognitive beliefs about the self and the environment in these youngsters. Evidencing an interaction between positive schizotypy symptoms and psychological distress in 22q11DS may also signal the reinforcing effect symptoms of delusions and hallucinations exercise on threat-related beliefs and negative schemas about the self. In turn, reinforced beliefs can retroactively promote further psychological distress and potentiality for the expression of positive schizotypy symptoms (see Figure 2). Both clinical studies with 22q11DS adolescents found increased social isolation in relation to positive schizotypic manifestations in youths with the deletion syndrome. This may be indicative that youngsters with 22q11DS may also signal the reinforcing effect symptoms of delusions and hallucinations exercise on threat-related beliefs and negative schemas about the self. In turn, reinforced beliefs can retroactively promote further psychological distress and potentiality for the expression of positive schizotypy symptoms (see Figure 2). Both clinical studies with 22q11DS adolescents found increased social isolation in relation to positive schizotypic manifestations in youths with the deletion syndrome.20,21 This may be indicative that youngsters with delusions interpret social interactions in a way that increases delusional distress, which in turn promotes social withdrawal. Future research on metacognitive beliefs in 22q11DS may hold interesting clues to our understanding of psychosis-proneness and the unfolding of positive symptoms in youngsters with the deletion syndrome.

Conclusions

In this selective review, we wished to examine the basic factors that lead to the manifestations of positive symptoms of psychosis in youngsters with 22q11DS. We only briefly touched on the genetic factors, reviewed elsewhere in the literature. Instead, we focused on reuniting the evidence from studies reporting schizophrenic-like symptoms, neuroanatomical alterations, emotional disorders and cognitive dysfunctions in youths with 22q11DS, and on proposing a
multifactorial account that outlines the different routes psychosis-proneness may employ in the unfolding of clinically relevant psychotic phenomena. We feel that the high prevalence of schizophrenia in 22q11DS is best represented by the wealth of risk factors associated with the neurogenetic syndrome in terms of genetic, neuroanatomical, cognitive and affective concerns. Clearly, more investigations concerning the multiple risk-factor interactions are necessary, some of which may investigate complex processes such as brain maturation and the unfolding of hallucinations, while others further examine higher-order cognitive functions such as social cognition in relation to the elaboration of a delusional belief system. These may yield preventative treatment strategies that acknowledge the expression of psychotic symptoms in youths with 22q11DS but help to prevent their development into clinical states of psychosis.

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